Patterns of primary care consultation for physical symptoms in parents and children: an epidemiological study

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Ph.D.

Date of submission October 2013

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Degree for which thesis being submitted: Doctor of Philosophy

Title of thesis: Patterns of primary care consultation for physical symptoms in parents and children: an epidemiological study

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Date of submission:
Original registration date: 28/09/2009
Name of candidate: Mujahed Shraim
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Abstract

Non-specific or medically unexplained physical symptoms (MUPS) are common among children, persist in considerable proportions of those affected, and can lead to primary care consultations. A systematic review in this thesis has provided limited evidence of an association between MUPS in parents and children.

This thesis has investigated the association between GP consultation for MUPS in 5417 parent-child pairs registered with 12 GP practices, and examined whether this is related to persistent GP consultations for MUPS in children. One descriptive study, two case-control studies, and one prospective cohort study were conducted using GP electronic medical records.

In children, the annual GP consultation prevalence for MUPS was 21%, and 12% of all consultations were for MUPS. A significant association was found between consultations for MUPS in mothers and children (adjusted OR 1.42, 95% CI 1.24, 1.63). No association was found between fathers and children, but the association was stronger when both parents consulted for MUPS (adjusted OR 1.52, 95% CI 1.19, 1.93). Significant dose-response relationships were found between numbers of consultations for MUPS and numbers of MUPS in mothers and children. These associations were clearest in maternal-child consultations for painful MUPS and MUPS in specific bodily systems including gastrointestinal, musculoskeletal and neurologic MUPS.

Over a quarter (27%) of children who consulted for MUPS at baseline had persistent GP consultations for MUPS at one-year follow-up. Exposure to maternal

consultations for MUPS was associated with persistent consultations for similar symptoms in children (adjusted RR 1.29, 95% CI 1.05, 1.58). Exposure to maternal consultations for painful, gastrointestinal, and neurologic MUPS was associated with persistence consultations for similar MUPS in the child.

This thesis provides important information about the impact of parental health on child health and consulting behaviour. The implications for primary care and future research are highlighted.

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Acknowledgments

All praise is due to Allah.

I would like to thank my supervisors Dr Kate Dunn, Professor Christian Mallen, and Dr Milisa Bucknall for their contribution to this thesis.

I am greatly indebted to Dr Kate Dunn for proposing this PhD project and for her invaluable advice and constructive feedback throughout the development of this thesis.

Thanks to Dr Kelvin Jordan for his support and advice. Thanks also to Rhian Hughes, Claire Ashmore, and Joanne Bailey for their organisational support.

I would also like to thank other people who have been involved; Ian Thomas, Tracy Whitehurst, Dr Paul Campbell, Dr Majid Artus, Jacqueline Gray, Sue Weir, Ashley Ford, and Kelly Barnett.

Many thanks to the NHS for funding my PhD.

Also, I would like to thank my friends for their encouragements; Dr Riyad Khanfer, Dr Diyaa Rachdan, Dr Feras Mustafa, Dr Yousof Balawi, and Basem Al-Omari.

Many thanks to my mother, brothers, and sisters for their support.

Many thanks to my father and mother in law for their encouragement.

Many thanks to my wife Widad Shraim and my sweetheart sons Al-Bara and Osama for their support, and for being so patient with me.

Dedication

To my mother Fathieh Faris Odeh

To the memory of my father Mahmoud Ahmad Shraim

Publications arising from this thesis

- Mujahed Shraim, Christian D Mallen, Kate M Dunn. GP consultations for medically unexplained physical symptoms in parents and their children: a systematic review. *British Journal of General Practice*; 63(610): e318-e325.
- Mujahed Shraim, Milisa Bucknall, Christian D Mallen, Kate M Dunn. The association between GP consultations for non-specific physical symptoms between parents and children: a case-control study. (In preparation).
- Mujahed Shraim, Milisa Bucknall, Christian D Mallen, Kate M Dunn. Prognosis of GP consultations for non-specific physical symptoms in children: a prospective cohort study. (In preparation)

Glossary

ATC	Anatomical Therapeutic Chemical Classification System for drugs
BNF	British National Formulary
CBT	Cognitive Behavioural Therapy
CFS	Chronic Fatigue Syndrome
CI	Confidence Intervals
CiPCA	Consultation in Primary Care Archive
CSSD	Complex Somatic Symptoms Disorder
DiPCA	Demographic and Deprivation Data in Primary Care Archive
DoB	Date of Birth
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, 5th edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder, 4th edition
ECG	Electrocardiography
EMIS	Egton Medical Information System
FAP	Functional Abdominal Pain
GERD	Gastro-oesophageal Reflux Disease
GHS	General Household Survey
GP	General Practitioner
GPRD	General Practice Research Database
HSCL	Hopkins Symptom Checklist
IBS	Irritable Bowel Syndrome
ICD-10	The International Statistical Classification of Disease and Related Health Problems, 10th revision
ID	Identification
IMD	Index of Multiple Deprivation
LBP	Low Back Pain
LSOA	Lower Layer Super Output Area
MiPCA	Medical Certificates in Primary Care Archive
MUPS	Medically Unexplained Physical Symptoms
NHS	National Health Services
NSLBP	Non-specific Low Back Pain
ONS	The Office for National Statistics

OPCS	Classification of Interventions and Procedures
OR	Odds Ratio
P	P-value
PiPCA	Prescriptions in Primary Care Archive
RAP	Recurrent Abdominal Pain
RiPCA	Referrals in Primary Care Archive
RR	Relative Risk
SD	Standard Deviation
X^2	Chi-squared Test

Chapter 1. Introduction

This thesis is concerned with the study of primary care consultation patterns for medically unexplained MUPS (MUPS) in children, with particular reference to the association of GP consultations for MUPS between parents and children, and the prognosis of GP consultations for MUPS in children. This introductory chapter provides a definition for MUPS and MUPS. The importance of conducting research on children presenting with MUPS in primary care is highlighted. The rationale for the thesis is discussed, and the research question, aim, and specific objectives of this thesis are then stated. Finally, this chapter concludes with an outline of the contents of subsequent chapters in this thesis.

1.1. Medically unexplained physical symptoms

Within this thesis MUPS are defined as physical symptoms that lead the patient to seek healthcare, and after clinical assessment, do not seem to be explained by a clearly defined cause or a defined medical disease (Nimnuan et al., 2001a, Melville, 1987). MUPS, such as musculoskeletal pain, abdominal pain, headache, and fatigue are common in the community, and are among the most frequent reasons for visiting a general practitioner (GP). Research findings indicate that around 19% and 22% of all patients consulting in primary care have one or more MUPS for at least three and six months, respectively (de Waal et al., 2004, Peveler et al., 1997).

MUPS in patients presenting in primary care are very important, not only because they are common, but also because a considerable proportion of patients

presenting with MUPS suffer substantial psychological distress, functional impairment, and have a poor quality of life as a result of their MUPS (Jackson & Kroenke, 2008, Kroenke et al., 1997).

Additionally, several studies have demonstrated that patients presenting with MUPS represent a significant burden to healthcare as a result of frequent GP consultations, repeated medical diagnostic testing, prescriptions, and referrals to speciality clinics (Jackson & Kroenke, 2008, Fink et al., 1999, Fink, 1992). Furthermore, MUPS can impact on society as a whole. For instance, in the year 2002, it was estimated that MUPS accounted for 10-15% of all disability pensions in Denmark (Stenager et al., 2003).

In the light of these findings, epidemiological research aiming at identifying and better understanding the risk factors associated with MUPS among patients presenting in primary care is needed in order to improve health outcomes and quality of life for those patients, as well as reduce healthcare costs.

1.2. Why consider research on children with MUPS in Primary Care?

Research findings indicate that MUPS are common among children and persist in a considerable proportion of those affected over time (El-Metwally et al., 2004, Perquin et al., 2003, Hotopf et al., 1998). Additionally, MUPS in children are associated with frequent utilisation of health care services, functional impairment and restriction in daily living activities, and negative impact on the quality of life of both children and their parents (Gold et al., 2009, Watson et al., 2003, Hunfeld et al., 2002). Children with MUPS are also at greater risk of developing other MUPS

and common psychiatric disorders such as anxiety and depression in adulthood (Hotopf et al., 1998, Mallen et al., 2009, Campo, 2007).

The causes of MUPS among children are still poorly understood. Several epidemiological studies have reported that MUPS among children may be related to a number of factors, including stressful events related to schooling and social relationships (Berntsson & Gustafsson, 2000, Eminson et al., 1996), psychopathology (Saps et al., 2009, Egger et al., 1999), childhood abuse and neglect (Fiddler et al., 2004, Goodwin et al., 2003), and pubertal development (Virtanen et al., 2009).

Other epidemiological studies have examined the relationship between parental MUPS and child MUPS. Results from such studies suggest that parental health, particularly MUPS, is related to the health of the child. A cross-sectional study showed that parents with MUPS and / or anxiety or depression were more likely to have children with high primary care attendance rates, and were also more likely to perceive their children to have MUPS (Little et al., 2001). A birth cohort study reported that the presence of MUPS at age 36 was related to self-reported poor parental health earlier in life (at age 15) – the analysis compared the most symptomatic 5% with the rest (Hotopf et al., 1999). A case-control study in primary care found that children of mothers with chronic somatisation disorder (MUPS for at least two years) were more likely to have MUPS and higher GP attendance rate than children of mothers with explained chronic illness or mothers without chronic illness (Craig et al., 2002). Another study set in secondary care reported that parental MUPS were associated with increased MUPS in their children with chronic abdominal pain (Walker et al., 1994).

Other researchers have examined the association of painful MUPS between parents and their children, and reported mixed findings. A population-based cohort study found that recurrent/persistent abdominal pain in children was associated with poor health and emotional disorder in their parents (Hotopf et al., 1998). In another study based in secondary care, mothers of adolescents with juvenile primary fibromyalgia syndrome reported twice as many pain conditions and significantly greater depressive symptoms than mothers of comparison peers (Kashikar-Zuck et al., 2008). Also, a population-based study found a link between self-reported maternal and child pain (Saunders et al., 2007). By contrast, two population-based cross-sectional studies found no significant association between parental and child pain (Jones et al. 2004), and non-specific low back pain (NSLBP) (Balague et al., 1995). Additionally, one case-control study in primary care did not find a significant association between history of irritable bowel syndrome (IBS), migraine and somatoform disorder in mothers and GP attendance for functional abdominal pain (FAP) in their children (Campo et al., 2007).

Prior research shows that children's encounters with GPs correlate with those of parents and are influenced by the prevalence of chronic illness and psychological stability in parents (Johnsen et al., 1988). A primary care study in 10 GP practices from Australia reported that high levels of maternal stress and numbers of GP consultations, in addition to the child health status, were significant predicators of the child’s GP attendance rate (Ward & Pratt, 1996). In another study, Ward and colleagues found significant associations for GP practice attendance rate and hospital admission rate between mothers and their children (Ward et al., 2006).

The exact mechanism underlying these associations is not fully clear, but seems to be multifactorial. Research evidence suggests that genetic factors may contribute to the onset of some MUPS such as headache and IBS (Larsson et al., 1995, Morris-Yates et al., 1998). The findings of other studies indicate that shared environmental factors such as parental conflict or divorce (Huurre et al., 2006, Troxel & Matthews, 2004) and low socio-economic status (Ostberg et al., 2006, Groholt et al., 2003, Berntsson et al., 2001) may contribute to familial aggregation of illness. Other studies suggest that childhood social learning of illness behaviour plays important role in the development of MUPS and functional somatic syndromes (Levy et al., 2007, Cardol et al., 2007, Levy et al., 2000).

Only a few studies have examined the relationship between MUPS in parents and children, and their findings were inconsistent. Most of those studies examined this relationship for specific MUPS (e.g. FAP and NSLBP) in children of different age groups, and relied on self-report data. So far, it is not clear whether an association exist between documented GP attendance for the whole spectrum of MUPS in parents and children across age range.

1.3. Thesis rationale

Previous research has provided limited evidence of an association between MUPS in parents and their children. Additionally, prior research has found significant correlation between GP attendance rates in parents and children. However, it is not clear whether this association is specifically present for GP consultations for MUPS. As MUPS are a significant burden in primary care, it is important to know if parental GP consultation for MUPS is a risk factor for similar

GP consultations in their children. Identifying and better understanding of factors influencing GP attendance for MUPS among children is important. Furthermore, research investigating the impact of parental MUPS on the healthcare and prognosis of the child is lacking. Further research examining such patterns would provide evidence of the role of parental MUPS experience on the health and GP consultation patterns of the child. This may provide insights into more appropriate management strategies for children presenting in primary care with MUPS, which could improve health outcomes, quality of life, and, ultimately, reduce healthcare costs. Such information may also shed light on measures that might help in preventing the development or recurrence/persistence of MUPS among children.

1.4. Thesis aims and objectives

This research aims to investigate the association between GP consultations for MUPS in parents and their children.

Specific objectives are:

1. To carry out a systematic review of literature to identify and summarise the results of observational studies, based in primary care or community settings, examining the association of GP consultations for MUPS between parents and children.
2. To describe the epidemiology of MUPS in children in primary care.
3. To conduct a case-control study in primary care to:

a. Investigate whether GP consultations for MUPS in children are associated with previous exposure to GP consultations for MUPS in their parents.
b. Explore whether the influence of parental GP consultation patterns for MUPS on the child GP consultation patterns for MUPS is different for mothers and fathers.
c. Examine the association between GP consultations for specific MUPS in the child and previous exposure to parental GP consultations for the same MUPS.

4. To conduct a prospective cohort study to investigate the prognosis of GP consultations for MUPS tom in children, and assess whether exposure to maternal GP consultation for MUPS is associated with persistent GP consultations for MUPS in children.

1.5. Outline of subsequent chapters

- **Chapter 2. Background to MUPS in children.** This chapter provides a definition for the concept of MUPS and related terms. It also gives an overview of current diagnostic classification systems for MUPS, burden of MUPS in primary care, and epidemiology of MUPS in children in the general population and primary care settings.
- **Chapter 3. Background to methods.** This chapter discusses the definition and key principles of epidemiology, including descriptive and analytical epidemiology, case-control studies, cohort studies, prognostic studies, and interpretation of observational studies.

- **Chapter 4. The association between GP consultations for MUPS in parents and their children: a systematic review.** This chapter presents the findings of a systematic review of observational studies examining the association between GP consultations for MUPS in parents and their children.
- **Chapter 5. General study design:** This chapter presents the general study methods and operational definitions used in this thesis.
- **Chapter 6. The epidemiology of MUPS among children in primary care:** This chapter presents the findings of an epidemiological study describing the prevalence of GP consultation for MUPS in children, the most common presenting MUPS, and the characteristics of children consulting with MUPS.
- **Chapter 7. The association between GP consultations for MUPS in parents and children: a case-control study.** This chapter presents the findings of a case-control study which investigates whether GP consultations for MUPS in children are associated with previous exposure to GP consultations for MUPS in their parents, and whether this association is different for mothers and fathers.
- **Chapter 8. The association between GP consultations for specific MUPS in mothers and children: a case-control study:** This chapter presents the results of a case-control study examining the association between GP consultations for specific MUPS in children and previous exposure to maternal GP consultations for the same MUPS.
- **Chapter 9. Prognosis of GP consultations for MUPS in children: a prospective cohort study:** This chapter presents the results of a prospective cohort study which investigate the prognosis of GP consultations for MUPS in

children, and examine whether exposure to maternal GP consultations for MUPS is associated with persistent GP consultations for MUPS in children.

- **Chapter 10. Discussion:** This chapter summarises the main findings of this thesis, and discusses the strengths, limitations, generalisability, and implications for primary care and future research.

1.6. Summary

Prior research has demonstrated that MUPS are common among children and tend to persist into adulthood, and that MUPS are associated with functional impairment, increased utilisation of healthcare services, and greater risk of psychiatric disorders during adulthood. Few studies have provided limited evidence for an association between GP consultations for MUPS in parents and their children.

Identifying the risk factors associated with GP consultations for MUPS in children is important, because this has implications for the management and prevention of MUPS among children presenting in primary care.

More research using documented GP consultation data is needed to examine the association between GP consultations for MUPS in parents and children across the whole spectrum of MUPS and child age groups.

This thesis will examine the association between GP consultations for MUPS in parents and children using GP electronic records, and investigate the prognostic factors associated with persistent GP consultations for MUPS in children.

This chapter has presented the outline of subsequent sections. The following chapter defines the concept of MUPS and gives an overview of current diagnostic classification systems for MUPS and their limitations. It also describes the burden and epidemiology of MUPS in children in the general population and primary care settings.

Chapter 2. Background to MUPS

2.1. Introduction

This chapter provides an overview of MUPS and their epidemiology in children. It is not intended to provide an extensive review of the literature, but aims to provide a background to research presented in this thesis. The first sections of this chapter focus on the definition of MUPS, the concept of MUPS, diagnostic classification systems for MUPS, and the impact of their limitations on primary care. The subsequent sections give an overview of the epidemiology of MUPS in children.

2.2. Physical symptoms

Most people, at some point in their lives, experience different physical symptoms, and seek medical help because of physical symptoms. The word "symptom", from the Latin symptōma and from the Greek sumptōma, is defined by the American Heritage Dictionary as "a characteristic sign or indication of the existence of something else." (The American Heritage Dictionary of the English Language, 2012). The word "symptom" has been long used in medicine where it is defined as "subjective evidence of disease or physical disturbance observed by the patient." (Merriam-Webster Online Dictionary, 2013). Physical symptoms are generally referred to as 'physical symptoms' in general medicine and 'somatic symptoms' in psychiatry. In this context, the words 'physical' and 'somatic' mean

“of or relating to the body as distinguished from the mind or spirit.” (The American Heritage Medical Dictionary, 2007).

Physical symptoms can occur in all bodily systems, and one way of classifying physical symptoms is to group them into three main types: pain at different locations (e.g. musculoskeletal pain, abdominal pain, headache), functional disturbance in different bodily systems (e.g. dizziness, palpitations, constipation), and complaints of fatigue or exhaustion (Henningsen et al., 2007).

Physical symptoms are common in the community, and most people manage their symptoms without seeking medical care. One study reported that 80% of Americans, including children, experience physical symptoms in any given month and about one quarter of them seek healthcare due to physical symptoms (Green et al., 2001). The majority of patients who seek healthcare for their symptoms are seen and managed in the primary care setting (Green et al., 2001, Kroenke, 2003). Research shows that physical symptoms are self-limited in the majority of patients presenting in primary care (Kroenke & Jackson, 1998). In this study, 70% of patients who presented with physical complaints improved by two weeks follow-up and, of those who had not, 60% recovered at three months follow-up. However, about one quarter of patients who present in primary care with physical symptoms experience persistent or recurrent physical symptoms as long as five years (Jackson & Passamonti, 2001).

Some physical symptoms are secondary to the direct effects of injury and others are a manifestation of physical diseases or psychiatric disorders. Many physical complaints, such as abdominal pain, headache, fatigue and musculoskeletal pain, are common presentations of psychiatric disorders such as

anxiety and depression (Campo et al., 1999, Simon et al., 1999, Kirmayer & Robbins, 1991). However, many physical complaints remain medically unexplained due to lack of evident cause or pathological changes on physical examination and diagnostic medical testing. Medically unexplained MUPS (MUPS) are defined as physical symptoms that lead the patient to seek medical help, and after clinical assessment, do not seem to be explained by a clearly defined cause or a diagnosis of a defined medical disease (Nimnuan et al., 2001a, Melville, 1987). In the UK, Nimnuan and colleagues (2001a) examined medical records and diagnostic tests results of new patients attending seven speciality clinics and found that 52% of patients had at least one MUPS. Another study in the USA followed patients presenting with 14 common MUPS in a primary care clinic over a three-year period, and reported that organic aetiology was established in only 16% of the cases; symptoms in 10% of cases were classified as psychological; and in 74% of cases the aetiology remained unknown (Kroenke & Mangelsdorff, 1989).

The causes of MUPS are poorly understood, but most are likely to be a multi-causal problem, with both physical and psychological factors interacting (Mayou, 1991). Many psychobiological mechanisms and models have been hypothesised to contribute to MUPS, but none of those mechanisms and models has been able to provide a comprehensive explanation (Brown, 2004). In a review of psychological mechanisms and empirical evidence for the development and maintenance of MUPS, different aspects have been highlighted as relevant, including cognitive and behavioural aspects, emotional regulation, personality, and attachment style (Rief & Broadbent, 2007). Table 2.1 presents the psychological and psychobiological mechanisms that may contribute to development of MUPS as summarised by Reief and Broadbent (2007, p.836).

Table 2.1. Mechanisms involved in MUPS

Possible precursors of MUPS	**Sample reference**
Over-exclusive concept of health	Barsky et al. (1993)
Traumatic experiences	Golding (1994)
Family member with chronic illness during childhood	Stuart & Russell (1999)
Attachment style, neuroticism	Noyes et al. (2003)
Former experiences with pain and symptoms	Bayer et al. (1997)
(Modern) health worries	Noyes et al. (2005); Petrie et al., (2005); Winters et al. (2003)
Aspects of symptom development and maintenance	
Increased awareness of physical sensations; body scanning	Rief, Hiller et al. (1998)
Perception of physical sensations; sensory filtering problems	James et al. (1990)
Attribution of physical sensations as possible illness signs	Hitchcock and Mathews (1992)
Missing distraction	Bantick et al. (2002); Pennebaker (1982)
Expectation of physical sensation & Generalization of triggering stimuli	Lorenz et al. (2005)
Health anxiety, illness worry	Jackson and Passamonti (2005)
Erroneous memory for illness probabilities	Rief et al. (2006)
Negative doctor-patient encounter is associated with failing reassurance; dissatisfaction increases health care use	Rief and Nanke (2004)
Multiple causal illness beliefs, but organic explanations dominate the scene and predict health care use	Rief and Nanke (2004)
Partners (and doctors?) confirm organic illness beliefs	Butler et al. (2001)
Operant conditioning of illness behaviour and reassurance seeking	Salkovskis & Warwick (1986); Sullivan et al. (2004)
Negative affectivity reduces symptom tolerance	Meagher et al. (2001)
Neural sensitisation, reduced neural filtering, brain plasticity	Basbaum and Jessell (2000)
Development of “pain and symptom schemata” in the brain	Pincus and Morley (2001)
Chronic stress conditions and immunological aberrations are associated with hyperalgesia and illness behaviour	Fries et al. (2005)
Involvement of the serotonergic system in pain perception	Basbaum & Jessell (2000); Rief et al. (2004); Russo et al. (2003)

Source: Reief and Broadbent (2007, p.836)

To characterise and diagnose patients presenting with health complaints, medical practitioners use diagnostic classification systems, based on predefined symptom checklists, such as the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) and Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM-IV) (Mayou et al., 2005).

Mayou and colleagues discuss that diagnostic classifications of illnesses provide constructs to aid communication, provide relevant prognostic information, and guide treatment and rigorous research (Mayou et al., 2005).

Current diagnostic classifications systems (ICD-10 and DSM-IV) classify MUPS either under psychiatric disorders or as syndrome diagnoses categorised as general medical complaints (World Health Organisation, 1992). In psychiatry, most MUPS are classified under the somatoform disorders categories of the DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organisation, 1992). Somatoform disorders include somatization disorder, undifferentiated somatoform disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, and somatoform disorder not otherwise specified.

Wessely and colleagues (1999) argue that classifying these diagnostic categories under the somatoform disorders does not suggest that these disorders share common aetiological or causal factors; rather, this classification was based on the grounds of clinical utility. These disorders share the common characteristic that MUPS are not sufficiently explained by a general medical condition, by effect of a substance, or by another mental disorder, and the symptoms must cause clinically significant distress or functional impairment (American Psychiatric Association, 1994). These diagnoses are differentiated solely by the type, number and duration of MUPS experienced by the patient.

In general medicine, however, MUPS are classified as functional somatic syndromes, such as IBS, fibromyalgia, and chronic fatigue syndrome (CFS) (Wessely et al., 1999). Functional somatic syndromes are simply differentiated by clusters of different MUPS that suggest shared underlying dysfunction of a specific

bodily system that relate to a particular medical speciality (Brown, 2007). Table 2.2 presents clusters of common MUPS and common diagnostic labels given to them by different medical specialties (Brown, 2007).

2.3. Shortcomings of current classification systems for MUPS

Research evidence suggests that MUPS exist on a continuum of severity, ranging from transient and mild MUPS to persistent and disabling MUPS (Jackson & Passamonti, 2001, olde Hartman et al., 2009, Katon et al., 1991). A particular problem in primary care is that somatoform disorder categories (summarised in box 2.1) only include the minority of patients with chronic multiple MUPS and offers no opportunity for the classification of majority of primary care patients who present with a single or few MUPS of short duration (Rosendal et al., 2007). Additionally, many authors argue that contemporary classification of MUPS under the somatoform disorder has both theoretical and clinical limitations. First, somatoform disorder categories evolved in specialised settings and tend to include severe and chronic cases and therefore are of little use in primary care (Fink et al., 2005). In fact, several studies have demonstrated that a formal somatoform disorder diagnosis is relatively rare in the primary care setting (see table 2.3). Second, some diagnostic categories for somatoform disorder are poorly and arbitrarily defined and lack the support of empirical evidence, and, therefore, considerable overlap was found between different diagnostic categories (Mayou et al., 2005, Brown, 2007, Fink et al., 2005, Escobar et al., 2002, Widiger & Clark, 2000). Third, somatoform disorder requires the MUPS to be fully unexplained by an underlying organic disease or when an organic disease is present, the MUPS

or functional impairment should be incompatible with it based on physical examination and diagnostics testing (American Psychiatric Association, 1994).

Table 2.2. Common MUPS and diagnostic labels by medical specialty

Specialty	Common MUPS	Common diagnostic labels
Psychiatry	Depends on referral source	Somatoform disorder, Somatization disorder
Gastroenterology	Abdominal pain; diarrhoea; bloating; constipation; excessive flatulence	Irritable bowel syndrome; non-ulcer dyspepsia
Cardiology	Chest pain; palpitations; fainting	Non-cardiac chest pain; Atypical chest pain
Neurology	Gait disturbance; headaches; seizures; sensory disturbance; paraesthesias	Non-epileptic attack disorder; conversion disorder
Rheumatology	Joint pain; fatigue; headaches sleep disturbance	Fibromyalgia
Infectious diseases	Fatigue; headaches; poor concentration; joint pain	Chronic (postviral) fatigue syndrome (aka myalgic encephalomyelitis)
Dentistry	Facial pain; headaches; tinnitus	Atypical facial pain; Temporomandibular joint disorder
Ear, nose and throat	Lump in throat; breathing problems	Globus syndrome
Allergy	Fatigue; burning eyes; breathlessness; poor concentration; weakness; dizziness	Multiple chemical sensitivity
Respiratory medicine	Breathlessness; rapid breathing	Hyperventilation syndrome
Gynaecology	Pelvic pain; pain during sex; dysmenorrhea; painful urination; urinary retention	Chronic pelvic pain
Military medicine	Fatigue; headaches; muscle pains; neurological symptoms; poor concentration	Gulf war syndrome

Source: Brown (2007, p.770)

Box 2.1. DSM-IV Somatoform Disorder categories

Somatization Disorder: is a polysymptomatic disorder that begins before age 30 years, extends over a period of years, and is characterized by a combination of pain, gastrointestinal, sexual, and pseudoneurological symptoms.

Undifferentiated Somatoform Disorder: is characterized by unexplained physical complaints, lasting at least 6 months, that are below the threshold for a diagnosis of Somatization Disorder.

Conversion Disorder: involves unexplained symptoms or deficits affecting voluntary motor or sensory function that suggest a neurological or other general-medical condition. Psychological factors are judged to be associated with the symptoms or deficits.

Pain Disorder: is characterized by pain as the predominant focus of clinical attention. Also, psychological factors are judged to have an important role in its onset, severity, exacerbation, or maintenance.

Hypochondriasis: is the preoccupation with the fear of having, or the idea that one has, a serious disease on the basis of the person's misinterpretation of bodily symptoms or bodily functions.

Body Dysmorphic Disorder: is the preoccupation with an imagined or exaggerated defect in physical appearance.

Somatoform Disorder, Not Otherwise Specified: is included for coding disorders with somatoform symptoms that do not meet the criteria for any of the specific Somatoform Disorders.

Source: APA (1994)

Table 2.3. Prevalence of somatoform disorder categories in adults in primary care

DSM-IV Somatoform Disorder Categories					
Study (sample size)	Somatization Disorder	Undifferentiated Somatoform Disorder	Hypochonderiasis	Chronic pain	Conversion Disorder
Smith 2005 (206)	1.5[a]	18.9	1.9	1.0	0.5
de Waal 2004 (437)	0.5	13.0	1.1	1.6	0.2
Fink 1999 (99)	1.0	27.3	4.0	8.1	3.0

[a]Figures are percentages

However, to assess whether physical symptoms are medically unexplained or not is complicated and may be unreliable, especially in patients with comorbid medical conditions (Rief & Rojas, 2007, Kroenke et al., 2007). For example, a

Danish primary care study found a large variation between GPs from 27 general practices in the rate of diagnoses of MUPS, with a prevalence rate ranging from 3% to 33%, even after accounting for variations in prevalence rates across GP practices (Rosendal et al., 2003). Fourth, classification of MUPS under the somatoform disorder states that the cause of the MUPS is a mental disorder, yet the cause is not well understood and most likely to be multifactorial (Mayou, 1991, Fink et al., 2005, Sharpe & Mayou, 2004). Fifth, the term "somatoform" is related to the term "somatization", which is defined by Lipowski as "a tendency to experience and communicate psychological distress in the form of somatic symptoms" (Lipowski, 1988), a definition that has been rejected by many patients (Stone et al., 2002). Sixth, epidemiological studies have demonstrated that MUPS are prevalent among children, but, the somatoform disorder criteria are not applicable to the vast majority of children because they require the incidence of at least one sexual or reproductive symptom (Eminson, 2007, Postilnik et al., 2006). The prevalence of somatoform disorder among children in primary care is unknown. However, studies in the community (Lieb et al., 2000) and secondary care settings (Bisht et al., 2008) have reported that somatoform disorder categories are very rare among children in (see table 2.4). Moreover, healthcare seeking behaviour by children should be viewed within the family context, which take into account the family's health beliefs, attitudes and parental influence (Eminson, 2007). Finally, somatoform disorder requires patients to recall their MUPS over the course of their lifetime, which is certainly difficult and may be unreliable, especially in children (Rief & Rojas, 2007, Simon & Gureje, 1999). For example, a large international primary care study examined the stability of somatization disorder diagnosis and recall of somatization symptoms over one

year and found that half of MUPS reported by patients at baseline were not remembered after one year (Simon & Gureje, 1999).

Table 2.4. Prevalence of somatoform disorder categories in children in the community and secondary care

	DSM-IV Somatoform Disorder Categories				
Study (sample size)	Somatization disorder	Undifferentiated somatoform disorder	Hypochondriasis	Pain disorder	Conversion disorder
Lieb 2000 (3021)	0.0[a]	6.7	0.0	1.9	0.3
Bisht 2008 (17500)	0.0	0.2	0.0	0.0	0.4

[a]Figures are percentages

The DSM-IV is currently under review and one of the proposed changes concerns the content and labelling of somatoform disorders categories. In the proposed revisions and draft criteria for the DSM-5 categories, the DSM-5 workgroup proposes the diagnosis of complex somatic symptoms disorder (CSSD) as a replacement for somatoform disorder categories (American Psychiatric Association, 2011). Box 2.2 summarises the proposed diagnostic criteria for CSSD.

The proposed CSSD has advantages over the format of somatoform disorder categories as CSSD incorporates a quantitative approach and reflects both somatic and psychological symptoms severity and, therefore, may increase its validity and clinical utility (Dimsdale et al., 2009). However, the complex or simple somatic symptoms disorder categories do not necessary apply to many primary care patients, because confirming the cognitive distortion criterion of the CSSD

(criterion B) may not be easy, especially among children (see box 2.3). In addition, the proposed CSSD has not yet been finalised and its validity and clinical utility are still to be determined.

Box 2.2. Proposed diagnostic criteria for CSSD and simple somatic symptom disorder in DSM-5

Complex Somatic Symptom Disorder (CSSD)

To meet criteria for CSSD, criteria A, B, and C are necessary.

A. Somatic symptoms: one or more somatic symptoms that are distressing and/or result in significant disruption in daily life.

B. Excessive thoughts, feelings, and behaviors related to these somatic symptoms or associated health concerns: At least two of the following are required to meet this criterion:

(1) High level of health-related anxiety.

(2) Disproportionate and persistent concerns about the medical seriousness of one's symptoms.

(3) Excessive time and energy devoted to these symptoms or health concerns.

C. Chronicity: Although any one symptom may not be continuously present, the state of being symptomatic is chronic (at least 6 months).

Simple Somatic Symptom Disorder

This diagnosis requires the following 3 criteria:

A. Somatic Symptoms: one or more somatic symptoms that are distressing and/or result in significant disruption of daily life

B. Excessive thoughts, feelings, and behaviors related to these somatic symptoms or associated health concerns: This diagnosis requires one of the following:

(1) Disproportional and persistent thoughts about the seriousness of one's symptoms

(2) High level of anxiety about health or symptoms

(3) Excessive time and energy devoted to these symptoms or health concerns

C. Symptom duration is greater than 1 month

Source: American Psychiatric Association (2011)

The classification of MUPS as functional somatic syndromes has been a topic of much debate. One of the principal questions that have been raised is whether these functional somatic syndromes represent separate entities and whether they share common risk factors (Wessely et al., 1999, Fink & Schroder, 2010, Fink et

al., 2007, Nimnuan et al., 2001b, Aggarwal et al., 2006, Deary, 1999). Wessely and his colleagues (1999) argue that the existence of specific somatic syndromes is largely an artefact of medical specialisation, rather than any real differences in clinical features between MUPS patients. They provide comprehensive evidence that there is a substantial overlap in the case definitions of functional somatic syndromes, and therefore patients with one functional somatic syndrome frequently meet diagnostic criteria for other syndromes. A large body of research has also provided evidence that functional somatic syndromes have much in common and, therefore, are better conceptualised as one single syndrome (Fink & Schroder, 2010, Fink et al., 2007, Nimnuan et al., 2001b, Aggarwal et al., 2006, Deary, 1999).

Up to now, there is no agreement between diverse medical specialties on the best diagnostic construct for MUPS patients. Consequently, current classification systems for MUPS leave the majority of primary care patients with MUPS undiagnosed (Rosendal et al., 2007). Also, it has been argued that conducting rigorous research and developing evidence-based management strategies for patients presenting in primary care with MUPS are hampered by lack of appropriate and agreed classification systems (Peveler et al., 1997, Rask et al., 2009, Kroenke, 2006, Rosendal et al., 2005).

2.4. Terminology

At present, it appears that there is little agreement between researchers and clinicians from diverse medical settings on the most appropriate term to describe MUPS that arise without evident organic pathology. Several terms are used to

refer to these symptoms, such as “hysteria”, “hysterical”, “conversion”, “dissociation”, “somatization”, “psychogenic”, “psychosomatic, “functional symptoms”, “functional somatic symptoms or syndromes” (such as IBS and CFS), and “MUPS” (Brown, 2007, Deary, 1999, Rosendal et al., 2005). Many of these terms are used in psychiatry and imply that the cause of MUPS is psychological; and, therefore, these terms have been found to be unsatisfactory and refused by many patients (Stone et al., 2002). In their study, Stone and colleagues (2002) reported that the term ‘functional’ was more acceptable to patients. Brown (2007) discusses that patients are often more comfortable with terms that imply that the cause of MUPS is a medical rather than a psychological, such as various “functional somatic syndromes”. However, the term “functional” indicates altered function of the nervous system, which is usually viewed as medically explained (Trimble, 1982). Also, various terms related to functional somatic syndromes imply a physical cause for the symptoms, which often lacks direct evidence (Brown, 2007). Some authors prefer the term ‘MUPS’ for its impartial perspective with respect to aetiology of MUPS (Eminson, 2007, Burton, 2003). However, other authors and experts argue that the term ‘MUPS’ is unsatisfactory as it encourages a dualistic mind set between psychiatry and general medicine in relation to aetiology of MUPS (Kroenke et al., 2007, American Psychiatric Association, 2011, Rosendal et al., 2005). However, the term “MUPS” is most commonly used in primary care literature (Peveler et al., 1997, Salmon et al., 2007, Salmon et al., 2009). So, to overcome any terminological confusion and for the purpose of research presented within this thesis, the term “medically unexplained physical symptoms” will be used within in this thesis. Within this thesis physical symptoms are defined as physical symptoms which are not medically explained, that lead the

patient to seek medical help to refer to physical symptoms without a clear pathology after clinical examination. The operational definition for MUPS used in this thesis is presented in chapter 5 (see section 5.5)

2.5. Burden of MUPS

Identification and classification of patients presenting with physical symptoms is a prerequisite for further management, and failure to diagnose and treat patients presenting with physical symptoms may result in consequences for patients, healthcare systems, and the society (Fink et al., 2005). In primary care, the majority of patients with MUPS present with few symptoms of short duration, and therefore their complaints are often recorded as symptom diagnoses (Rosendal et al., 2007). These patients are often managed by prescribing symptomatic treatment and systematic investigation to exclude physical cause (Mayou, 1991). However, symptomatic treatment has been met with limited success despite negative diagnostic tests and reassurance, which is frustrating for both patients and GPs (Kroenke et al., 1990, Kroenke et al., 1997). GPs often find management of these patients challenging (Salmon et al., 2005, Wileman et al., 2002). This is reflected by the type of "labels" used by GPs to refer to these patients, such as "problem, difficult, or dysphoric patient" (Mathers et al., 1995), "heart sink patients" (Rosendal et al., 2005), and "helpoholic patients" (Epstein et al., 1999). Patients also become frustrated by not receiving any convincing explanation for their persistent symptoms and perceive the care they receive by their GPs as unsatisfactory (Dirkzwager & Verhaak, 2007). Therefore, simple reassurance is often unsuccessful in patients with MUPS (Rief et al., 2006).

MUPS are problematic for many patients especially when they become chronic. MUPS are associated with significant functional impairment, poor quality of life, and comorbid psychiatric disorders (de Waal et al., 2004, Dirkzwager & Verhaak, 2007, Stanley et al., 2002, Katon & Walker, 1998, Kroenke et al., 1994, Smith et al., 2009). In the UK, a primary care study of patients presenting with MUPS found that about 70% of patients reported that MUPS interfered "very much to quite a lot" with their life and what they can do (Stanley et al., 2002). Another primary care study in the USA demonstrated that the presence of any MUPS was associated with significant functional impairment (Kroenke et al., 1994).

Many patients with MUPS consume health care disproportionately, including frequent consultations, unnecessary drugs, repeated investigations, and multiple referrals to speciality clinics. In the USA, patients with MUPS have more GP visits, more outpatients' visits, more emergency department visits and more hospital admissions than patients without MUPS, with estimated annual healthcare costs of $256 attributed to MUPS alone (Barsky et al., 2005, Barsky et al., 2001). Another study from the USA showed that patients with IBS have higher healthcare costs for both gastrointestinal (GI) and non-GI problems than control subjects (Levy et al., 2001). The economic burden of adolescent chronic pain alone in the UK is £8000 per child per year, with the overall national economic burden of chronic pain being £3840 million in one year (Sleed et al., 2005). A study from the UK reported that MUPS account for a significant proportion of consultations by frequent consulters in 12 speciality clinics (Reid et al., 2001). In this study, the proportion of frequent consulters with MUPS ranged between 54% in gastroenterology clinics to 2% in dermatology clinics. In another study of frequent consulters with MUPS in most speciality clinics in the UK, outcomes as measured by psychiatric morbidity,

repeated consultation, and functional impairment remained poor at three year follow-up (Reid et al., 2003). MUPS also have a significant impact on health care resources and society in general. Data from Denmark showed that in the year 2002 MUPS accounted for 10-15% of disability pensions (Stenager et al., 2003).

2.6. Epidemiology of MUPS in children

2.6.1. Incidence and prevalence of MUPS

Prevalence estimates of MUPS among children differ markedly across studies due to differences in methods, type and number of MUPS, the defining criteria for MUPS (e.g. definition and measurement of pain used), and age of participating children. Nevertheless, the majority of such epidemiological studies do agree that MUPS are common among children in the general population. One epidemiological study from the UK investigated the lifetime prevalence of 32 MUPS and illness attitudes in 805 school children aged 11 to 16 years (Eminson et al., 1996). Eminson and her colleagues (1996) reported that the median number of MUPS in girls was six (range 0 to 22) and boys had a median of five MUPS (range 0 to 22), with 8.3% of children having 13 or more MUPS. In the USA, a population based study of 36 MUPS in 540 children and adolescents found that more than half of children reported at least one MUPS and more than 15% reported four or more MUPS in the past two weeks (Garber et al., 1991).

Table 2.5 presents the prevalence of specific MUPS from selected population-based studies. The results of these studies indicated that headache, abdominal

pain, back pain, and fatigue are the most common MUPS in children (see table 2.5).

There are few studies on MUPS among children in the primary care setting and in particular there is a lack of studies reporting on the incidence and prevalence of multiple MUPS among children presenting to primary care. The majority of data on prevalence of GP consultation for MUPS in children come from population-based studies using self-reported data by children or parents. The prevalence of GP consultations for MUPS among children reported by selected population and primary care based studies are summarised in tables 2.6. As shown in table 2.6, the self-reported one-year prevalence of GP consultation for abdominal pain ranged between 46% and 70%, and the lifetime prevalence of GP consultation for low back pain (LBP) in children ranged between 11% and 14%. Based on primary care medical records, the three-year prevalence of GP consultation for musculoskeletal pain and painful conditions in children was 6% and 31%, respectively.

Table 2.5. Prevalence of specific MUPS in children

Study	Country	Study design	Age (year)	Sample size	Time frame	Headache	Abdominal pain	Back pain	Dizziness	Fatigue	Chest pain	Leg/arm pain
El-metwally 2007	Finland	Retrospective	9-13	1756	1 week	29%	31%	4%	-	30%	3%	-
Brun Sundblad 2007	Sweden	Cross-sectional	9-13	1908	1 week	13%	7%	-	-	16%	-	-
Garber 1991	USA	Cross-sectional	7-17	540	2 weeks	28%	16%	16%	10%	23%	10%	10%
Berntsson 2001	Nordic countries	Cross-sectional	7-12	3760	2 weeks	13%	11%	2%	1%	-	-	-
Groholt 2003	Nordic countries	Cross-sectional	7-17	6230	2 weeks	15%	8%	5%	2%	-	-	-
Deomenech-Liaberia 2004	Spain	Cross-sectional	3-5	807	2 weeks	17%	39%	17%	2.2%	20%	-	17%
Vila 2009	UK	Cross-sectional	11-16	1173	2 weeks	66%	43%	40%	-	49%	41%	-
Eminson 1996	UK	Cross-sectional	11-16	805	Life-time	32%	29%	8%	42%	-	30%	32%

Table 2.6. GP consultation prevalence for MUPS in children

Study	Country	Setting	Study design	Age (year)	Sample size	MUPS	Data source	GP consultation Prevalence (Duration)
Salminen 1984	Finland	Community	Cross-sectional	11-17	370	Neck/back pain	Parents/child	60.7% (life-time)
Balague 1994	Switzerland	Community	Cross-sectional	8 -16	1716	LBP[a]	Parents/child	10.7% (life-time)
Balague 1995	Switzerland	Community	Cross-sectional	12-17	615	LBP	Child	14% (life-time)
Perquin 2000	The Netherlands	Community	Cross-sectional	0-18	6424	Painful conditions	Parents/child	57% (3 months)
Perquin 2001	The Netherlands	Community	Cross-sectional	0-18	254	Chronic pain	Parents/child	31.1% (3 months)
Boey 2001[a]	Malaysia	Community	Cross-sectional	9-15	143	RAP[b]	Child	45.5% (one year)
Boey 2001[b]	Malaysia	Community	Cross-sectional	9-15	161	RAP	Child	48.4% (one year)
Roth-Isigkeit 2005	Germany	Community	Cross-sectional	4-18	749	Painful conditions	Parents/child	50.9% (3 months)
Schwille 2009	Germany	Community	Cross-sectional	3-17	15241	RAP	Parents/child	44% (3 months)
Venepalli 2006	USA	Community	Cross-sectional	9-12	117	Multiple MUPS	Parents/child	70.8% (one year)
Devanarayana 2008	Sri Lanka	Community	Cross-sectional	5-15	734	RAP	Parents	70% (one year)
Masiero 2010	Italy	Community	Cross-sectional	12-16	7542	MSK[c] pain	Child	74.2% (one year)
Huang 2000	Australia	Primary care	Cross-sectional	3 -17	734	RAP	Parents	34% (one year)

Study	Country	Setting	Study design	Age (year)	Sample size	MUPS	Data source	GP consultation Prevalence (Duration)
van Eekelen 2002	The Netherlands	Primary care	Retrospective	0-18	200	Painful conditions	Medical records	31% (3 years)
de Inocencio 1998	Spain	Primary care	Retrospective	3-15	317	MSK pain	Medical records	6% (3 years)
de Inocencio 2004	Spain	Primary care	Retrospective	3-15	1000	MSK pain	Medical records	6% (3 years)
Levy 2006	USA	Primary care	Cross-sectional	8-17	334	RAP	Parents/child	12% (3 months)
Cardol 2006	The Netherlands	Primary care	Retrospective	1-12	65671	Multiple MUPS	Medical records	28% (one year)
Chitkara 2007	USA	Primary care	Prospective	0-5	5718	Multiple MUPS	Medical records	11% and 19% made 3 or more GP consultations for abdominal pain or constipation by age 5, respectively

[a]Low back pain; [b]Recurrent abdominal pain; [c]Musculoskeletal;

2.6.2. Impact of MUPS

Existing research examining the impact of MUPS in children indicates that MUPS are associated with significant distress and functional disability. Studies have consistently demonstrated that significant proportions of children suffer psychological distress and significant negative impact on most aspects of quality of life as a result of MUPS. MUPS were found to persist in a considerable proportion of affected children over time (El-Metwally et al., 2004, Perquin et al., 2003, Hotopf et al., 1998), and more often are associated with a greater risk of developing other MUPS (Ramchandani et al., 2005, Hunfeld et al., 2001), an increased risk of psychological disorders (Saps et al., 2009, Ramchandani et al., 2007, Merlijn et al., 2006), substantial functional impairment, poor overall quality of life of affected children and their families, and increased utilisation of healthcare services (Gold et al., 2009, Hunfeld et al., 2002, Campo et al., 1999, Domenech-Llaberia et al., 2004, Roth-Isigkeit et al., 2005, Oostenbrink et al., 2010). For example, in a population based cohort study of 13,971 British children (Ramchandani et al., 2005), recurrent abdominal pain (RAP) was significantly associated with the occurrence of other MUPS and higher rates of anxiety in children (adjusted odds ratio (OR) 2.12, 95% confidence intervals (CI) 1.70 to 2.65) and their mothers (adjusted OR 1.75, 95% CI 1.30 to 2.36). A further cohort study in the USA reported that abdominal pain persisted for over 4 weeks in 52% of affected children, and that abdominal pain was associated with higher anxiety and depression scores, poor overall quality of life, school absenteeism, and parental restrictions in social life (Saps et al., 2009). Another study from the Netherlands showed that chronic pain among adolescents was significantly

associated with poor self-reported quality of life, greater incidence of other MUPS, and restrictions in daily living activities of both children and their parents (Hunfeld et al., 2001).

2.6.3. Prognosis

Existing research indicates that significant proportions of children presenting with MUPS continue to experience multiple MUPS and have increased risk of developing common psychiatric disorders later in life. A 2-year population based follow-up study of Dutch children found that 48% and 30% of children who complained of chronic benign pain at baseline had persistent pain at one-year and two-year follow-up, respectively (Perquin et al., 2003). A population based Finnish study (El-Metwally et al., 2004) showed that children with musculoskeletal pain at baseline had about three times higher risk of recurrent musculoskeletal pain at 4-year follow-up (adjusted OR 2.9, 95% CI 1.9 to 4.4). Another Finnish study also reported that widespread pain recurred in almost one third of children at 4-year follow-up (Mikkelsson et al., 2008). In this study, independent predictors of future recurrence of widespread pain were older age, female gender, depressiveness and back pain symptoms. A UK population-based prospective study found children who reported behavioural problems or MUPS at baseline were at an increased risk of developing widespread pain at 1-year follow-up (Jones et al., 2003a).

Children with MUPS were also found to be at greater risk of developing other MUPS, functional impairment, and anxiety and depressive disorders in adulthood. In the UK, a nested case-control study within a birth cohort study showed that experiencing abdominal pain and illness in the family during childhood is

associated with greater risk of reporting MUPS in adulthood (Hotopf et al., 1999). A population based birth cohort study from the UK reported that headache complaints in childhood were significantly associated with increased risk of headache complaints (adjusted OR 2.22, 95% CI 1.62 to 3.06), multiple MUPS (adjusted OR 1.75, 95% CI 1.46 to 2.10), and symptoms of psychiatric disorders in adulthood (adjusted OR 1.41, 95% CI 1.20 to 1.66) (Fearon & Hotopf, 2001). A cross-sectional population-based study found that pain experiences in childhood in both the child and the family were associated with greater risk of psychiatric disorders, such as anxiety and depression, during adulthood (Mallen et al., 2009).

As shown in table 2.6, previous research has demonstrated that primary care presentation with MUPS among children is extremely common. What is less clear is whether children presenting to primary care with MUPS have recurrent or persistent GP consultations for MUPS over time. The limited data from primary care and the findings of several epidemiological studies in the community and secondary care settings suggest that children with MUPS are likely to continue to consult for MUPS during childhood and later in adulthood. In the USA, a cohort study of children from birth to 5 years of age found that primary care presentation for Gastro-oesophageal Reflux Disease (GERD), abdominal pain, and constipation is significantly associated with repeated medical consultations (Chitkara et al., 2007). In the UK, a case-control study in a single general practice showed that experiences of ill health and adversity in childhood are independent significant predictors of frequent attendance in adulthood, even after controlling for adult psychiatric disorders (Kapur et al., 2004). Another study from the UK reported that childhood adversity was significantly associated with frequent medical consultations at outpatients at neurology, cardiology, and gastroenterology clinics

in adult life (Fiddler et al., 2004). In this study, the observed association between childhood adversity and frequent medical consultations in patients with MUPS was mediated by the number of MUPS attributed to the illness. Finally, British children who reported RAP in childhood were more likely to report other MUPS, and had greater risk of unexplained hospital admissions during adulthood (Hotopf et al., 1999, Hotopf et al., 2000).

2.6.4. Factors associated with the prevalence of MUPS

2.6.4.1. Age, gender, and pubertal development

Data from population-based studies indicate that the prevalence of MUPS increases with age among children and adolescents, peaking in late childhood and early adolescence (Virtanen et al., 2009, Jones et al., 2003a, Petersen et al., 2006, Roth-Isigkeit et al., 2004, Watson et al., 2002, Perquin et al., 2000a). Previous research examining the association between GP consultation for MUPS and age, using either self-reports or medical records, reported conflicting findings. Children in the younger age group had significantly higher attendance rate compared to older children in some studies (Little et al., 2001, Perquin et al., 2000b, Boey & Goh, 2001c), whereas other studies reported that GP attendance for MUPS increased with age (Roth-Isigkeit et al., 2005, Roth-Isigkeit et al., 2004, Levy et al., 2004). The reason for this inconsistency is not clear. However, these studies relied on self-reported data and included different age groups, which may be one explanation.

Existing population-based studies investigating the relationship between reporting of MUPS and gender in children have also shown mixed findings. Some studies reported that girls had significantly higher prevalence of MUPS than boys (Berntsson et al., 2001, Watson et al., 2002, Perquin et al., 2000b). Conversely, a 5-year longitudinal cohort study of back pain in adolescents in UK showed that back pain was more common in boys than girls (Burton et al., 1996). Other studies found no statistically significant association between gender and the prevalence of MUPS in children (Berntsson & Gustafsson, 2000, Chitkara et al., 2007). Likewise, the majority of existing studies examining the association between gender and childhood attendance for MUPS did not show a significant difference in consultation rates for MUPS between the two sexes (Perquin et al., 2000b, Boey & Goh, 2001c, Perquin et al., 2001, Boey & Goh, 2001a, Masiero et al., 2010, Campo et al., 2004, van Eekelen et al., 2002).

Some studies have assessed the relationship between reporting of MUPS and pubertal development. A cohort study investigating the effect of timing of puberty on reporting of psychosomatic symptoms among Finish girls aged 14 to 16 showed that early developing girls reported more MUPS than on-time and late developing girls (Aro & Taipale, 1987). A cross-sectional study of 20,000 adolescents in USA demonstrated that early and late time developers reported more MUPS than on-time developers (Rhee, 2005). The observed association between pubertal development and reporting of MUPS was more common in girls than boys (Virtanen et al., 2009, LeResche et al., 2005).

2.6.4.2. Psychosocial factors

Several population-based studies found an association between MUPS in children and the psychiatric characteristics of the child such as conduct problems (e.g. restlessness, anger, disobedience, irritability and violence) and hyperactivity (Berntsson & Gustafsson, 2000, Berntsson et al., 2001, Berntsson & Kohler, 2001, Jones et al., 2003b, Faull & Nicol, 1986). Other studies found an association between reports of low back pain in children and particular life-style characteristics during childhood, such as smoking, heavy duties or jobs during leisure time, and lack of physical fitness and development (Feldman et al., 2001, Harreby et al., 2001, Harreby et al., 1999).

Stressful events stemming from school-related problems (e.g. low academic achievement, dissatisfaction with school, and poor social contacts with peers) were also associated with reporting of MUPS (Berntsson & Gustafsson, 2000, Eminson et al., 1996, Faull & Nicol, 1986), or GP consultation for MUPS (Perquin et al., 2000b). In the Netherlands, children and adolescents with lower education levels had significantly more GP consultations for painful conditions than their peers with higher education levels (Perquin et al., 2000b).

Children from certain socio-economic backgrounds, such as divorced parents, parents with a sense of incoherence, single-parent families, low educated families, low income families, and families with lack of social support had higher prevalence and number of MUPS than children from more advantaged families (Huurre et al., 2006, Ostberg et al., 2006, Groholt et al., 2003, Berntsson et al., 2001, Juang et al., 2004). Similarly, other studies found a significant association between child

attendance in primary care for MUPS and socioeconomic status (Ferrin et al., 2009), council house tenancy (Little et al., 2001), non-intact families, families with lower levels of parental education and minority ethnic groups (Campo et al., 1999). Conversely, some studies found no statistically significant association between GP consultations for MUPS among children and specific family and parental characteristics such as parental education level and occupation (Little et al., 2001, Campo et al., 1999, Boey & Goh, 2001c, Perquin et al., 2001, Boey & Goh, 2001a), family income or socioeconomic status (Little et al., 2001, Boey & Goh, 2001c, Perquin et al., 2001, Boey & Goh, 2001a, Campo et al., 2004). Likewise, no statistically significant relationships were found between child attendance in primary care for MUPS and family size (Perquin et al., 2001), number of children in the family (Boey & Goh, 2001c, Boey & Goh, 2001a), parental gender (Levy et al., 2000), or parental marital status (Little et al., 2001, Perquin et al., 2001).

Campo et al. (2007) found maternal age to be inversely related to child attendance with abdominal pain, whereas Perquin et al. (2001) found no significant association between parental age and presentation of childhood chronic pain in primary care. Likewise, birth order (first child in the family) was associated with child attendance with MUPS in primary care (Garralda & Bailey, 1987), but this association was not found to be statistically significant by another study (Perquin et al., 2001).

2.6.4.3. Childhood adversity

Few studies have examined the association between adverse childhood experiences, such as physical and sexual abuse, and reporting of MUPS during

childhood. In USA, a prospective population-based study of 845 children who were followed up from the age of 4 to12 years reported a link between physical abuse and GI MUPS (van Tilburg et al., 2010). Another study of adolescents with migraine from Taiwan showed that adolescents who suffered from physical abuse had higher frequency of headache and depressive symptoms than adolescents who did not report physical abuse (Fuh et al., 2010).

2.6.4.4. Psychopathology

Several population-based studies have provided evidence for an association between MUPS and significant psychological disorders in children and adolescents (Saps et al., 2009, Rimes et al., 2007, Mikkelsson et al., 1999, Hyams et al., 1996). Data from population-based studies indicate that the experience of multiple MUPS seems to be a marker for severity of depressive disorders (Bohman et al., 2010, Larsson, 1991). A multi-symptom Swedish study reported that adolescents with depressive disorders experienced more MUPS compared to controls, and also demonstrated that the duration and severity of depression were significantly associated with the number of MUPS experienced by adolescents (Bohman et al., 2010).

Other studies in primary care also suggest that psychopathology is significantly associated with child attendance in primary care with MUPS (Campo et al., 1999, Campo et al., 2004, Garralda & Bailey, 1987). In the UK, children identified by GPs as having psychological factors contributing to their primary care presentation were significantly more likely to present with more MUPS than control children (Garralda & Bailey, 1987).

2.6.4.5. Level of functional disability and coping strategies

Existing literature indicates that functional disability due to MUPS and passive coping strategies play an important role in child attendance in primary care. Many studies reported significant positive associations between functional impairment (Campo et al., 1999, Perquin et al., 2001, Masiero et al., 2010, Campo et al., 2004), schools absence (Boey & Goh, 2001c, Boey & Goh, 2001a, Levy et al., 2006, Venepalli et al., 2006), and sleep problems due to MUPS and child attendance in primary care clinics (Boey & Goh, 2001a). Additionally, passive coping responses to MUPS were found to be associated with higher child attendance (Levy et al., 2004).

2.6.4.6. Child health status and MUPS characteristics

Several studies found a positive association between higher child attendance in primary care for MUPS and a number of factors related to the health status of children and the characteristics of their presenting MUPS. Increased numbers of medical conditions in children and having perceived poor health of the child by parents were reported as significant predictors of higher child attendance for MUPS in primary care (Little et al., 2001). Also, higher child attendance for MUPS was significantly predicted by pain intensity level (Roth-Isigkeit et al., 2005, Perquin et al., 2000b, Perquin et al., 2001, Boey & Goh, 2001a, Masiero et al., 2010), pain frequency (Perquin et al., 2000b, Perquin et al., 2001), and number of presenting MUPS (Fiddler et al., 2004).

2.6.4.7. Family influences

A large body of research has examined the occurrence of MUPS within families. The exact mechanism by which family influences the development of MUPS in the child is not fully clear, but research findings suggest that this is most likely to be a multi-causal effect. Data from genetic studies suggest that genetic factors may contribute to the onset of some MUPS or functional syndromes such as headache and IBS (Larsson et al., 1995, Morris-Yates et al., 1998). Other studies suggested that shared environmental factors such as parental conflict or divorce (Huurre et al., 2006, Troxel & Matthews, 2004) and low socio-economic status (Ostberg et al., 2006, Groholt et al., 2003, Berntsson et al., 2001) may contribute to familial aggregation of illness. Additionally, several studies have demonstrated that childhood social learning of illness behaviour plays an important role in the development of MUPS and functional somatic syndromes (Craig et al., 2002, Levy et al., 2007, Cardol et al., 2007, Levy et al., 2000).

Population-based studies investigating MUPS within families have shown conflicting results over whether an association exists between child and parental MUPS especially painful conditions. Some studies found an association between self-report of MUPS in parents and children (Balague et al., 1995, Borge & Nordhagen, 2000, Kovacs et al., 2003, Merlijn et al., 2003, Jones et al., 2004, Smith & Chambers, 2006). A study of 1000 British school children indicated that family members of children with RAP report more RAP and other MUPS than family members of children without RAP (Apley & Naish, 1958). A population-based study of 2466 children in the USA found that children were at increased risk of having back pain, headache, and abdominal pain if their mothers had the same

pain conditions or had pain at multiple sites (Saunders et al., 2007). However, other population-based studies found no significant association between MUPS in children and their parents. For example, one study found no significant association between site specific pain complaints (stomach, arms and legs, head, back and neck and shoulders) in parents and their children (Borge & Nordhagen, 2000). Similarly, a study of 1326 school children found no significant relationship between any pain, widespread pain, and LBP in parents and their children (Jones et al., 2004). The reasons for these contradictory findings in population-based studies are not clear. However, differences between studies with respect to types of studied MUPS, age groups, and study design may explain this.

Only a few epidemiological studies have examined the associations between GP consultations for MUPS in parents and children. Findings from such studies suggest an association between GP consultations for MUPS in parents and children (Little et al., 2001, Craig et al., 2002, Cardol et al., 2006a). The results and limitations of studies examining the association between GP consultations for MUPS in parents and children are discussed in more details in chapter 4.

2.7. Summary

This chapter has presented an overview of the existing literature on MUPS, including the definition and classification of MUPS, shortcomings of current classification systems for MUPS, MUPS burden, and the terms used to refer to MUPS and a justification for the use of the term “MUPS” in this thesis. Furthermore, this chapter has presented the epidemiology of MUPS in children. As discussed in this chapter, previous research has shown mixed findings with

respect to the association between GP consultation for MUPS between parents and children.

Chapter 3. Background to methods

3.1. Introduction

This chapter provides a background to the main epidemiological approaches used in this thesis. The chapter starts with a definition of epidemiology with an overview of the key principles of epidemiology and importance of epidemiologic approaches with respect to epidemiology of MUPS in Primary Care. The main aims of descriptive and analytical epidemiology are then presented. The strengths and weaknesses of GP consultation databases are described. Then definitions and use of incidence and prevalence measures are presented. Also descriptions of case-control, cohort, and prognostic studies are given. The last few sections address important aspects that need to be considered when interpreting the findings of observational studies, with particular reference to types of bias and causal inference.

3.2. Definition and key principles of epidemiology

The term epidemiology is derived from the Greek word “epidemeion” meaning “to visit”, which was used by Hippocrates to differentiate diseases visiting the community from other diseases that reside in it (Buck et al., 1988). According to Buck et al (1988), the word epidemiology was originally used as a term for investigation of epidemic diseases, and was first used in the late sixteen century by Angelerio, a Spanish physician, who published a study on plague entitled *Epidemiologia*.

One of the most frequently used definitions of epidemiology which encompasses several terms that reflect the basic principles and approaches of epidemiology is given by Porta:

"The study of the occurrence and distribution of health-related states or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control the health problems." (Porta, 2008, p.81).

This definition stresses that epidemiology is not only concerned with diseases, but also with all aspects of health with a primary aim to promote health in the population as a whole. In contrast with clinical medicine, epidemiology is concerned with study of populations rather than individuals, thus constituting the basic science of public health (Detels, 2002). However, epidemiology remains relevant to clinical medicine by enhancing the practice of medicine by providing better understanding of determinants of diseases and their management at both the individual and the population levels (Farmer & Lawrenson, 2004b).

Epidemiology is also concerned with quantifying the occurrence of disease and health-related states in the population. This information is then used by epidemiologists to further investigate and describe patterns of disease and health-related states in subgroups of the population in terms of age, sex, race, place, and other variables (Ahrens et al., 2005). Such data is needed to examine determinants of disease and other health-related conditions, which is considered as one of the most important roles of epidemiology (Ahrens et al., 2005). Epidemiology fundamentally assumes that disease is not randomly distributed in populations and that disease is influenced by causal and preventative factors,

thereby investigating this non-random distribution will shed light on risk factors for disease and potential underlying disease mechanisms (Detels, 2002).

In addition to communicable disease epidemiology, the scope of epidemiology has greatly enlarged over the years to include more epidemiological methods (e.g. surveillance, observation, hypothesis testing, analytic research, and experiments) to investigate causes and natural history of diseases; population health care needs assessment; development, assessment and evaluation of medical interventions, preventative programmes and health care services (Farmer & Lawrenson, 2004b, Porta, 2008).

The epidemiology of GP consultations for MUPS in children is important for many reasons. Quantifying the prevalence of children consulting with MUPS and measuring the proportion of their GP consultations for MUPS provide valuable information on commonness, duration, severity and impact of MUPS as well as utilisation of primary care services for MUPS. Also, investigating patterns of GP consultations for MUPS in terms of age, gender, and socioeconomic status, and other characteristics provides better understanding of factors influencing the decisions parents or children to consult for MUPS. More importantly, epidemiological investigation based on distribution and patterns of MUPS among children may ultimately help to identify risk factors associated with the development of MUPS, and also provide important data on outcomes of GP consultations for MUPS (e.g. prognosis). Such data can be very useful in developing better management strategies for children presenting with MUPS in primary care, and eventually may help in preventing the development or recurrence of MUPS.

3.3. Descriptive epidemiology

3.3.1. Description and use

Descriptive epidemiology aims to describe the occurrence and distribution of diseases and other health-related characteristics in populations according to three main epidemiologic descriptive variables: persons, place, and time (Porta, 2008). Descriptive epidemiologic studies provide information concerning the relationship of disease and health-related states to basic characteristics of population corresponding to these epidemiologic descriptive variables, such as age, gender, ethnicity, religion, occupation, socioeconomic status, education level, geographical location, and time of occurrence. In contrast to “analytic epidemiology”, descriptive epidemiology describes the occurrence and distribution of disease or health-related conditions according to basic characteristics of populations without testing particular hypotheses about causal relationships (Kelsey, 2010). However, descriptive epidemiologic studies may also have analytic scope (Porta, 2008).

Usually, descriptive epidemiologic studies use routinely collected health data (e.g. death certification data, hospital episode statistics, data from computerised GP practices, infectious disease notifications, and disease-specific registers) on disease exposure or disease outcomes (Parkin & Bray, 2005). The advantages of descriptive epidemiologic studies include that they are relatively cheap and relatively quick to complete, however, the data required for describing the distribution of disease in the population and relationship between disease and potential risk factors (e.g. data on exposure) may be incomplete or unavailable (Farmer & Lawrenson, 2004b).

Descriptive epidemiology plays an important role in realisation a number of key public health aims. Descriptive epidemiological studies provide important information about trends in health and disease including the magnitude and impact of diseases or health-related conditions on the population (Friis, 2010). They may be used to enhance our understanding of the natural history, clinical course, and mechanisms underlying diseases (Friis, 2010). Descriptive epidemiologic studies are also used to assess the healthcare needs of the population or subgroups of the population; such data is essential in order to plan health services, allocate resources appropriately, and evaluate the effectiveness of healthcare services and medical interventions (Farmer & Lawrenson, 2004b). Another important use for descriptive epidemiologic studies is that their results are used to generate hypotheses about potential risk factors and determinants of diseases; thus, stimulate and guide the development of analytical epidemiological studies (Kelsey, 2010, Saracci, 2010).

3.3.2. GP consultation databases

Around 97% of the UK population is registered with a GP (Department of Health, 2011). General practice is usually the first point of access to non-emergency healthcare in the UK. According to the Department of Health, about 90% of all patients' contacts with the National Health Service (NHS) occur in primary care settings (Department of Health, 2008). In most GP practices in the UK, clinical information about registered patients is recorded electronically, including information such as consultation data, treatments, diagnostic investigations, referrals, and other lifestyle characteristics, such as blood pressure,

body mass index, and smoking status. This routine and continuing collation of clinical data is not only an important source for assessing clinical practice and healthcare needs of the population but also an important source of information on morbidity, both diseases and symptoms, which occur in the population.

In contemporary epidemiologic research, GP consultation databases including anonymised patient medical records represent an important source of epidemiologic information, and have been widely used by researchers (The Lancet., 2001, no authors listed). In the UK, there are many GP research databases at both national (e.g. General Practice Research Database (GPRD)) and local levels (e.g. the Consultation in Primary Care Archive (CiPCA), West Midlands Local GP Research Databases). Although GP consultation databases provide an excellent source of information on morbidity occurring in the community, they have some limitations, and findings from epidemiological studies using such databases must be interpreted with caution (Farmer & Lawrenson, 2004b, Jordan & Croft, 2008). Table 4.1 outlines some strengths and weaknesses of GP research databases with respect to epidemiologic studies investigating morbidity and symptom-based conditions (Jordan & Croft, 2008, Jordan et al., 2006b).

Table 3.1. Main strengths and weaknesses for GP research databases

Strengths	Weaknesses
• Anonymised records • Include data from large patient populations • Information are collected routinely, thus provide a cost-effective source of epidemiological data • Can be used for longitudinal study of disease • Provide direct measure of healthcare use • Include data on consultation outcomes (e.g. diagnoses, prescriptions, referrals, diagnostic investigations) and some lifestyle characteristics, such as blood pressure, body mass index, smoking status. • Can be used to investigate linkages between different symptoms and diseases as well as other characteristics such as deprivation • Can be linked to survey data in the same populations • Morbidities can be coded as presenting symptoms (e.g. headache, abdominal pain, etc), with at least one code entered at each patient contact • Can be used to calculate disease incidence rates and annual prevalence rates of morbidities for all registered populations	• Data are collected primarily for clinical and routine use rather than specifically for research purposes • Caution is needed as to whether these represent real changes of prevalence or improvements in morbidity recording or changes in diagnostic criteria • They do not usually incorporate standardised criteria for applying diagnostic labels • The decision to use diagnostic labels reflect the GPs' habit or decision to refer the patient to special diagnostic investigation or specialty clinics • They only include data on treatments prescribed in general practice, thus over-the-counter medications and private therapies are unlikely to appear • GPs may not electronically record all patient contacts or code the reasons for those contacts • GPs may not record multiple problems during a consultation, only the most ''significant" or newest may be recorded • Identifying the first episode of morbidity (measuring incidence) is challenging because many patients do not have full coded histories or on computerised databases which may only have been running for a few years. Also, symptom-based conditions (e.g. musculoskeletal pain) do not always have a clear onset (first episode), therefore, the data is most likely to represent new or recurrent episodes of morbidity rather than the first ever episode. • Limited content on specific risk factors or exposures

Source: adapted from (Jordan & Croft, 2008, Jordan et al., 2006b)

3.3.3. Measures of MUPS frequency

Measures of MUPS frequency in the population provide key information needed to describe the amount of MUPS in a population and compare the amount of MUPS observed with another time, another group of people, or another place. The reason behind such comparisons is to try to understand why observed differences in frequency of MUPS exist, and thus learn more about MUPS and risk factors or determinants for development of MUPS. There are two main measures of frequency of MUPS in a population, incidence and prevalence.

3.3.3.1. Incidence

Incidence is defined as the number of new cases of disease that occur in a population over a defined period of time (Porta, 2008). Incidence is expressed as a rate, with a numerator (number of new cases of disease occurring in a defined period of time) and a denominator (number of people at risk of developing the disease over the same period of time). There are two measures of incidence commonly used, incidence risk and incidence rate (Kestenbaum, 2009d).

- Incidence risk = $\frac{number\ of\ new\ cases\ in\ time\ period}{number\ of\ people\ at\ risk\ at\ begining\ of\ time\ period}$
- Incidence rate = $\frac{number\ of\ new\ cases\ in\ time\ period}{number\ of\ person{-}years\ at\ risk}$

Incidence rates are of particular importance in studying disease aetiology, since they provide an accurate measure of risk for developing the disease in different groups of the population. Incidence requires a definition of when a susceptible person becomes a “case”, which can be a challenging task especially in poorly

defined conditions (Parkin & Bray, 2005). For example, identifying the first episode of a disease such as infectious diseases is often straightforward. However, many diseases or symptom-based conditions (e.g. musculoskeletal pain) are poorly defined and do not have a clear onset, in such situations, incidence often represents a measure of new episodes or recurrence rather than new cases of disease. Therefore, prevalence is the most commonly used measure for MUPS frequency in epidemiological studies.

3.3.3.2. Prevalence

Prevalence is usually a proportion and refers to how many people have a disease as opposed to those who do not have it. Prevalence is defined as the total number of people with an attribute or disease at a defined period of time divided by the total number of people at risk of having the attribute or disease at the same time period (Porta, 2008). Two measures of prevalence are commonly used, point prevalence and period prevalence (Farmer & Lawrenson, 2004c).

- Point prevalence = $\frac{number\ of\ people\ with\ a\ disease\ \ at\ a\ point\ in\ time}{Total\ population\ at\ same\ point\ time}$
- Period prevalence = $\frac{number\ of\ people\ with\ a\ disease\ at\ any\ time\ during\ a\ specified\ period}{average\ population\ over\ the\ same\ time\ period}$

Measurement of prevalence is particularly important in the case of chronic diseases, where new cases occur relatively infrequently, but the disease lasts a long time (e.g. rheumatoid arthritis). Such information is useful in the planning and allocation of health services (Kestenbaum, 2009d).

Prevalence is proportional to the incidence and duration of the disease; when both incidence and duration of the disease are stable, the relationship between prevalence and incidence can be expressed as: prevalence = incidence x average disease duration (World Health Organisation, 1989). Thus, prevalence will be higher for diseases which occur frequently or have a long duration (e.g. diabetes). Therefore, in the absence of useful incidence measures of diseases or conditions which do not have a clearly defined onset, such as MUPS, prevalence measures may be used to compare the risk of developing the disease between population subgroups (Parkin & Bray, 2005).

3.3.4. Types of descriptive epidemiologic studies

There are three main types of descriptive epidemiologic studies at individual level: case reports, case series, and cross-sectional studies. Case series and case reports fall beyond the scope of this thesis; therefore, this section will only focus on cross-sectional studies.

3.3.4.1. Cross-sectional studies

A cross sectional study is defined as "...a study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time." (Porta, 2008). In cross-sectional studies, both the disease status and exposure status are determined for each person in the study at a particular point in time (Parkin & Bray, 2005). Therefore, the relationship between the disease and potential risk

factors can be investigated either in terms of prevalence of disease among subgroups of the study population according to presence or absence of risk factors under the study, or in terms of presence or absence of the risk factor in both diseased and not diseased (Porta, 2008).

In cross-sectional studies, the prevalence rather than the incidence of disease or condition is used to investigate the relationship between the disease or the condition and potential risk factors. Thus, cross-sectional studies are unable to disentangle the direction of association between exposure and outcome, which is considered as one of the main disadvantages of cross-sectional studies (Kelsey, 2010, Kestenbaum, 2009d). Another disadvantage for cross-sectional studies is that they may distort the relationship between disease and exposure because the use of prevalence to measure disease is more likely to identify persons with a long duration of disease at a particular point in time than persons who die from the disease or recover quickly (Kelsey, 2010, Parkin & Bray, 2005).

3.4. Analytical epidemiology

3.4.1. Definition and use

One of the main uses of descriptive epidemiology is to develop hypotheses about determinants or potential risk factors that may influence the occurrence of a disease or a health-related condition. Analytical epidemiology is concerned with examining hypotheses about potential causal relationships, generated by descriptive epidemiologic studies, by using analytical methods (Porta, 2008). Usually, analytical studies proceed by assessing whether two or more groups with

mixed rates of disease or health-related conditions significantly differ according to presence or absence of potential risk factors (Bonita et al., 2006b). Potential risk factors may include age, sex, occupation, education level, socioeconomic status, personal lifestyle and behaviour, place of residence, etc. Analytical studies use statistical tests to examine hypotheses about causal relationships; however, any observed associations between disease and potential risk factors do not necessarily mean that the relationship is causal (Rothman et al., 2008b).

3.5. Case-control studies

3.5.1. Definition

A case-control study is defined as an observational study that examines the association between a disease, or an outcome, and potential risk factors by comparing individuals with the disease (cases) and individuals without the disease (controls) with regard to the frequency of previous exposures to potential risk factors of interest (Porta, 2008, Breslow, 2005). The main aim of case-control studies is to detect a relationship between previous exposure to a potential risk factor and an outcome, suggesting a hypothetical causal relationship (Kestenbaum, 2009a).

3.5.2. Case-control study design

The chief difference between case-control studies and cohort-studies is the way in which study subjects are selected. In case-control studies, the subjects are

selected based on presence or absence of disease or outcome under investigation and then their exposures to potential risk factors are ascertained retrospectively, whereas in cohort studies the subjects who are originally free of the disease or outcome are classified according to their exposure to potential risk factors and then followed over time to ascertain their disease or outcome status (Schlesselman & Stolley, 1982b).

The validity and generalisability of case-control studies depend on the way in which cases and controls are defined and selected, how exposure is measured, and how potential confounding variables are controlled for (Fletcher & Fletcher, 2005b, Schlesselman & Stolley, 1982a).

3.5.2.1. Identification and selection of cases

One of the fundamental prerequisite for ultimate identification and selections of cases is to define the disease and establish objective criteria which allow for reliable identification and diagnosis of cases to be made (Schlesselman & Stolley, 1982a). Another important issue in case definition is whether to include prevalent cases (existing cases) or restrict the study to incident cases (new cases). Fletcher and Fletcher (2005) argue for the use of incident cases because the potential risk factors for prevalent disease can be associated with incidence, duration of disease, or both, thereby the relative contributions of incidence and duration cannot be established. However, including only incident cases may not always be possible in conditions characterised by poorly defined onset, such as MUPS in children. This is because it can be very difficult to determine the timing and

occurrence of the first episode of MUPS regardless of the source of information used (medical records or self-report).

3.5.2.2. Selection of controls

As mentioned above (section, 3.5.2), the purpose of using a control group in case-control studies is to provide a comparative basis to assess the history of exposures to potential risk factors for the disease under investigation among cases and controls. The control group provides an estimate of the exposure prevalence which is expected to be found among cases if there was no relationship between exposure and disease in question (Schlesselman & Stolley, 1982a). Therefore, one of the most important principles in selection of controls is that controls should be selected from the same base population from which cases arise, and both groups should have an equal opportunity of being exposed to the potential risk factors for the disease of interest (Fletcher & Fletcher, 2005b, Grimes & Schulz, 2005). Failing to adhere to this basic principle is likely to result in selection bias which may threaten the validity of study results (dos Santos Silva, 1999a).

3.5.2.3. Sources of controls

There are several sources that can be used to obtain a control group, such as hospital controls, GP controls, neighbourhood controls, and random digit selection by telephone. However, to ensure comparability of cases and controls and eliminate the potential for selection bias, controls should be drawn from the same

underlying population as the cases (Kestenbaum, 2009a, Fletcher & Fletcher, 2005b).

3.5.2.4. Number of controls

Including several controls per case, especially when the number of cases is limited, is advisable (Fletcher & Fletcher, 2005b). Having several controls per case can provide more accurate estimation of the exposure frequency to risk factors under study among controls and increase the precision of the CIs for the estimated ORs, and thus enhances the statistical power of the study to detect associations of interest which truly exist (Kestenbaum, 2009a, Taylor, 1986). There is no specific set of rules about the optimal number of case per each case (Kestenbaum, 2009a). However, having more than four controls per case is inadvisable because it has little additional improvement in study power (Breslow, 1982).

3.5.3. Matching

Another fundamental aspect of case-control design is whether it is to be matched or not. Matching is a common approach which is used to control for confounding (Fletcher & Fletcher, 2005b). Confounding occurs when a second (or more) factor is associated with both the exposure of interest and, independently, with the disease under investigation, thereby the exposure-disease relationship become confounded with the effect of the confounding variable (Woodward, 1999). In case-control studies, the use of matching enhances the degree of similarity between cases and controls other than the potential risk factor of interest, thus any

observed relationship between the potential risk factor and disease cannot be attributed to the effects of these confounding variables (Schlesselman, 1982). Common matching variables include age, gender, place of residence, ethnicity, socioeconomic status, and other factors which are thought to be strongly associated with the exposure and the disease in question (Fletcher & Fletcher, 2005b, dos Santos Silva, 1999a).

Although matching is a powerful technique in dealing with confounding, Woodward (1999) discusses that matching has a number of potential disadvantages. First, it can be difficult to find suitable controls with increasing numbers of matching variables. Second, a matched-case-control design requires the use of special statistical analysis techniques that account for matching, which can be very complex to understand or compute. Third, once matching is done, the effect of matching variables on the risk of disease under study cannot be estimated. Fourth, the unadjusted effect of the primary exposure variable under investigation cannot be estimated without adjustment for the matching variables. Fifth, there is a risk of overmatching if matching is done incorrectly or unnecessarily, which may cause loss of efficiency or bias the findings.

3.5.4. Analysis of case-control studies

As mentioned above the principal aim of case-control studies is to estimate the magnitude of the association between a potential risk factor and a particular disease by comparing the frequency of previous exposure to the potential risk factor in both cases and controls. Therefore, the incidence rate of disease in exposed and unexposed individuals cannot be computed, and thus it is not

possible to directly estimate the relative risk (RR) of disease (Fletcher & Fletcher, 2005b). However, another measure of risk known as OR, which is similar to the RR, can be computed instead by dividing the odds of exposure in the cases by odds of exposure in the controls (dos Santos Silva, 1999a).

Statistical procedures used to analyse case-control studies (e.g. logistic regressions) calculate the ORs and their CIs (Greenberg et al., 2005a). If the OR and corresponding 95% CIs are above 1, this suggests a statistically significant association between the exposure and disease at 5% level of significance. If the OR and 95% CIs are less than 1, this indicates a statistically significant protective effect of exposure against the disease. If the lower limit of the CI is less than1 and the upper limit is greater than 1, this suggests that the OR is not significantly different from 1.

3.5.5. Advantages and disadvantages of case-control studies

The advantages and disadvantages of case-control studies are well described in epidemiological textbooks (Kestenbaum, 2009a, Schlesselman & Stolley, 1982b, dos Santos Silva, 1999a, Farmer & Lawrenson, 2004a). The main advantages and disadvantages of case-control studies are summarised in Table 3.2.

Table 3.2. Main advantages and disadvantages of case-control studies

Advantages	Disadvantages
Efficient in time and cost	Relies on recall or records for information and validation of information is often difficult or impossible
Requires comparatively fewer subjects	Control of confounding may be incomplete
Ideal to the study of rare diseases or those with long latency period	Recruitment and selection of appropriate controls can be difficult
Allows for the study of multiple potential risk factors	Usually cannot be used to determine the relative risk of disease in exposed and unexposed subjects
Involves no risk to subjects	Detailed study of mechanism is rarely possible

Source: Kestenbaum, 2009; Farmer & Lawrenson, 2004; dos Santos Silva, 1999; Schlesselman & Stolley, 1982

3.6. Cohort studies

3.6.1. Definition

Cohort studies are a particular type of analytical epidemiological study in which a group or groups of subjects are categorised according to their exposure to a potential disease risk factor, and are then observed over a period of time to compare the risks of developing the disease between exposed and unexposed subjects (Schlesselman & Stolley, 1982b). Prognostic or clinical cohort studies are discussed under section 3.7.

3.6.2. Cohort study design

Fletcher and Fletcher (2005) discuss that cohort studies can be carried out in two ways. One way is to assemble the cohorts of exposed and unexposed subjects to a potential disease risk factor in the present and then follow them up into the future to compare incidence rates of disease between cohorts (a prospective cohort study). The other way is to obtain information about the cohorts' historical exposures and then follow them up into the present when the disease outcome is already known (a historical cohort study or retrospective cohort study).

The process of conducting a cohort study can be summarised into three basic steps:

1. Choosing the cohort. As mentioned above, cohorts are selected and assembled based on their exposure to a potential risk factor. To maintain the temporal relationship between the exposure and the disease of interest, both exposed and unexposed individuals should be free of the disease (or outcome) at the beginning of the study (Kestenbaum, 2009b).
2. Follow up. The cohorts are then followed up over a sufficient period of time for the disease (or outcome) to develop (Fletcher & Fletcher, 2005c).
3. Measurement of outcome. The incident rates of disease in exposed and unexposed individuals are then compared to determine the relative risk of disease (or outcome) associated with exposure to the potential risk factor (dos Santos Silva, 1999b).

3.6.3. Analysis of cohort studies

As stated above, the RR is used as a measure for risk in cohort studies since we know the incident rates of disease (or outcome) in exposed and unexposed individuals. The RR is obtained by dividing the incidence rate of disease in exposed by incidence rate of disease in unexposed (Fletcher & Fletcher, 2005c). The X^2 test can be used to determine the statistical significance of the RR and calculate 95% CIs for the estimated RR (Greenberg et al., 2005a). The interpretation of the RR and 95% CIs is the same as for ORs in case-control studies (see section 3.5.4.).

3.6.4. Advantages and disadvantages of cohort studies

The main advantages and disadvantages of cohort studies are presented in table 3.3

Table 3.3. Main advantages and disadvantages of cohort studies

Advantages	Disadvantages
Allows for detailed description of disease associated with exposure, such as staging of disease and its natural history	Can be expensive and may require long duration of follow up, which can be difficult to maintain
Flexibility in selecting study variables and allows for comprehensive quality control of their measurements	Requires large sample size to study rare diseases
Ability to provide clear temporal relationship between exposure and disease so that the prospective cohort study design provides the strongest evidence for causality in observational studies.	Losses to follow up can affect the validity of the study
Allows for the study of multiple outcomes from a single exposure	Control of confounding effect may be incomplete

Advantages	Disadvantages
Allows for calculation of disease incidence rates in exposed and unexposed subjects	Exposure status and diagnostic criteria may change over time and lead to biased results

Source: Kestenbaum, 2009; Farmer & Lawrenson, 2004; dos Santos Silva, 1999; Schlesselman & Stolley, 1982

3.7. Clinical epidemiology

In contrast to classical epidemiology which is concerned with the study of the distribution and determinants of diseases in populations, clinical epidemiology is concerned with the study of a defined patient population (Bonita et al., 2006a). Fletcher and Fletcher (2005, p.3) define clinical epidemiology as “the science of making predictions about individual patients by counting clinical events in groups of similar patients in groups of similar patients and using strong scientific methods to ensure that the predictions are accurate”. The methods used in clinical epidemiologic studies are exactly the same methods used in classical epidemiology, but the characteristic that defines the subjects under study is a disease, health related condition, or a therapeutic intervention or a diagnostic procedure for the disease or health related condition (Weiss, 2008).

The main clinical issues addressed by clinical epidemiology include: definitions of normality and abnormality, accuracy of diagnostic tests, natural history and prognosis of disease, effectiveness of treatment, and prevention in clinical practice (Bonita et al., 2006a).

3.7.1. Prognosis and prognostic research

As stated above, prognosis of disease is one of the main issues addressed by clinical epidemiology. The term “prognosis” is defined as “the probability or risk of an individual developing a particular state of health (an outcome) over a specific time, based on his or her clinical and non-clinical profile” (Moons et al., 2009). In prognostic studies, the patient’s clinical and no-clinical profile or characteristics are used to predict the patient’s outcome of interest (Laupacis et al., 1994). The patient’s characteristics associated with the outcome under study are called prognostic factors (Bonita et al., 2006a).

3.7.1.1. Prognostic study design

Laupacis and colleagues (1994) argue that the cohort study design is the best design to investigate prognosis because it is difficult or unethical to randomise subjects according to different prognostic factors and that case-control studies are unable to provide information about the absolute risk of an outcome.

In prognostic studies, patients with a particular disease or a condition are assembled at the beginning of the study and prospectively followed up over sufficient period of time, and the number of outcome events of interests are then measured (Fletcher & Fletcher, 2005a). One important element of prognostic studies is that patients should be assembled to enter the study at a similar and well-defined point in the course of their disease, commonly at a time point close to the onset of disease or symptoms (Laupacis et al., 1994, Fletcher & Fletcher, 2005a). This point in time is called “zero time” and the group of patients

assembled at the “zero time” is known as inception cohort (Fletcher & Fletcher, 2005a). Ignoring this basic element in prognostic studies can lead to a different prognosis between patients, and thus may bias the study findings (Porta, 2008, Fletcher & Fletcher, 2005a).

One of the main problems in prognostic research on patients presenting with non-specific conditions, such as MUPS, in primary care is to identify and assemble a group of consulters at a similar and clearly defined point in the course of their MUPS. This is because MUPS are poorly defined with regard to their time of onset (McBeth & Jones, 2007). Researchers in the field of prognostic research on non-specific low back pain in primary care argue that it is very difficult or impossible to identify a group of patients with their first episode of low back pain and first GP consultation for this episode in order to provide an inception cohort (Hay & Dunn, 2009, Hestbaek et al., 2003). Also, they discuss that including patients with their first episode of low back pain runs the risk of selection bias against patients with recurrent or chronic low back pain, and limits the generalisability of findings to the whole spectrum of consulters seen in primary care. Therefore, it has been suggested that including consecutive consulters to study the prognosis of low back pain is more feasible and generalisable to patients seen in primary care settings (Hay & Dunn, 2009, Hestbaek et al., 2003). As discussed in the previous chapter (section 2.5.3), there is a lack of prognostic research on children presenting with MUPS in primary care. However, two systematic reviews of prognostic studies in adults with non-specific low back pain and general musculoskeletal conditions showed that the majority of studies that were conducted in primary care setting have included groups of consecutive consulters (Hestbaek et al., 2003, Mallen et al., 2007).

The main disadvantage of including consecutive children presenting with MUPS in primary care is that they may not be comparable according to the time of the onset of their MUPS. However, they are comparable in the sense that they are clearly identified and assembled at the time of their consultation for MUPS. Another advantage of studying a cohort of consecutive children consulting for MUPS is that they are likely to be representative of all children presenting MUPS in primary care, including both new and recurrent/persistent cases.

3.7.2. Interpretation of epidemiological studies

The main important issues that should be considered when interpreting the findings of epidemiological studies include the potential for either random or systematic errors in estimating the outcomes of interests and the criteria for causation (Rothman et al., 2008a, dos Santos Silva, 1999c). Any systematic errors in our estimates of association or other outcomes of interest due to errors in the study design, conduct, or analysis threaten the validity of the study (Greenberg et al., 2005b). The validity of a study has two components: internal validity and external validity (Rothman et al., 2008a). Internal validity refers to the degree to which an estimate is free from bias, which is considered prerequisite for external validity of a study (Rothman et al., 2008a). External validity (also known as generalisability) is concerned with the extent to which the conclusions drawn from a study are applicable or generalisable to other populations (target population) that were not included in the study (Porta, 2008).

Rothman et al. (2008) classify violations of internal validity into three major categories: confounding, selection bias, and information bias. The concept of

confounding was presented above under section 3.5.3. There are several types of biases that can be grouped under selection bias and information bias. Therefore, the particular types of bias relevant to this thesis are reviewed here.

3.7.3. Selection bias

Selection bias refers to the systematic difference in characteristics between subjects selected for a study and those who are not selected (dos Santos Silva, 1999a). This systematic difference may overestimate or underestimate the exposure-disease relationship or other outcomes of interest (Greenberg et al., 2005b). Selection bias is particularly important to consider in case-control studies, because cases and controls are selected after exposures have already occurred (Greenberg et al., 2005b). Hence, any systematic difference related to exposure between cases and controls may lead to a biased measure of association. Therefore, selected controls should be representative of the source population that gave rise to the cases in order to minimise the potential for selection bias (Rothman et al., 2008a).

In situations where a sample of available cohorts or cases and controls is selected for a study, the sampling method used should ensure that the selected subjects are representative of the source population to avoid selection bias, which can be achieved by a random selection of subjects (dos Santos Silva, 1999a).

3.7.4. Information bias

Information bias refers to the way that the data obtained on the groups being compared differs systematically (Greenberg et al., 2005b). One type of information bias is misclassification bias which results from recall bias, incorrect diagnosis, coding errors, or incompleteness of medical records leads to errors in measurement and ascertainment of study variables (Kleinbaum et al., 2007a, Kestenbaum, 2009e). There are two types of misclassification bias: non-differential misclassification and differential misclassification (Greenberg et al., 2005b).

Non-differential misclassification refers to misclassification of study data which occurs randomly across groups of study population (Kestenbaum, 2009e). Because the errors in non-differential misclassification occur randomly or roughly equally in measurement and ascertainment of the exposure or the outcome variables, the true relationship between exposure and outcome (if one exists) become obscure and the OR or RR diminish towards 1, which is known as “bias toward the null” (Greenberg et al., 2005b, Kestenbaum, 2009e).

In contrast to non-differential misclassification, differential misclassification occurs when the misclassification of either exposure or outcome differs systematically between groups of the study population (Kestenbaum, 2009e). Since this type of misclassification does not occur at random throughout the study groups, it can lead to spurious associations between the exposure and the outcome in either direction (dos Santos Silva, 1999a).

3.7.5. Criteria for causation

After considering the role of chance and potential effects of bias and confounding on any observed association, one of the most challenging questions that we should consider is whether the observed association is a causal one or not. In epidemiology, there is no formal method that can be used by epidemiologists to infer causality (Rothman et al., 2008b, dos Santos Silva, 1999c). However, one of the most popular set of criteria was proposed by Bradford Hill (Hill, 1965). Hill (1965) proposed nine aspects to be considered when assessing associations in observational studies, these include: strength of the association, consistency, specificity, temporal relationship, biological gradient, biological plausibility, coherence, experiment, and analogy. It is important to note here that these aspects are not sufficient to prove causation, but they may contribute towards causal inference. Hill (1965, p.11) states that “None of my nine viewpoints can bring indisputable evidence for or against the cause and effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”.

3.8. Summary

This chapter has provided a definition of epidemiology and presented the key principles. The main strengths and weaknesses of GP consultation databases were summarised. The main epidemiologic measures and study designs used

within this thesis, including their use, analysis, and advantages and disadvantages were discussed. The important aspects related to interpretation of observational studies, including sources of potential bias and criteria for causal inference were highlighted. The next chapter presents the findings of a systematic review summarising the literature on the association between GP consultations for MUPS between parents and children.

Chapter 4. The association between GP consultations for MUPS in parents and their children: a systematic review

4.1. Introduction

As discussed in chapters 1 and 2, there is emerging evidence of an association between the reporting of MUPS in parents and their children, but it is unclear whether this association is also present for GP consultations. There are no published systematic reviews summarising the research evidence on the association of GP consultations for MUPS between parents and their children. This chapter presents the findings of a systematic review of observational studies examining the association of GP consultations for MUPS between parents and their children.

4.2. Aims

The primary objective of this systematic review was to identify and summarise the results of published observational studies, based in primary care or community settings, examining the association of GP consultations for MUPS between parents and their children.

4.3. Methods

4.3.1. Search strategy

To identify relevant studies, MEDLINE, EMBASE, CINAHL and PsycINFO computerised bibliographic databases were searched, from their inception to October 2012, using the following search terms in titles and abstracts or as keywords: musculoskeletal diseases, pain, headache, tension-type headache, neck pain, shoulder pain, back pain, low back pain, abdominal pain, neuralgia, joint pain, somatoform disorders, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, medically unexplained symptoms, somatic symptoms, family, parents, adolescent, child, parent-child relation, child of impaired parents, primary health care, family health, primary health care, ambulatory care, community health services, child health services, family practice, family physician, physician's practice patterns, referral and consultation, epidemiology and observational studies. Appendix 1 presents a detailed search strategy for each database. No restrictions were imposed on the language of publication. References lists of all relevant papers were checked and their citations tracked using the Social Science Citation Index. Local experts were contacted to identify additional relevant studies. Awareness alerts were also created for each electronic database to ensure that new papers are identified as soon as they become available.

4.3.2. Study selection

Eligible studies were primary care and population based observational studies that investigated the association between GP consultations for MUPS, medical diagnosis of functional somatic syndromes, or history of treated MUPS in parents and GP consultations for MUPS in children aged 1 to 17 years. Studies were included if GP consultations data for MUPS was obtained using primary care medical records, self-reported data, or both data sources. This review included only studies in which MUPS were operationally defined as MUPS or specifically referred to as functional, somatic, or non-specific. Studies were included regardless of the time period over which these associations have occurred. Box 4.1 presents the exclusion criteria used in this review.

Box 4.1. Exclusion criteria used in the review

- Randomized controlled trials (RCTs), intervention studies, and small case series.
- Studies including participants with pain or physical symptoms resulting from specific medically explained diseases or trauma (e.g. Rheumatoid Arthritis, Diabetes, and Cancer)
- Studies including participants with specific diseases (e.g. HIV and diabetes).
- Studies not reporting GP consultation data for the parent or the child (e.g. studies only reporting symptoms in both).

Titles and abstracts of all studies were screened and irrelevant studies were excluded. Two reviewers (MS with KD or CM) assessed full-text papers to

determine the eligibility of studies that appeared to meet the inclusion criteria, or when a defined decision could not be made based on the title and/or abstract alone. Any disagreements were resolved by consensus or reconciled by a third reviewer.

4.3.3. Data extraction and quality assessment

Standardised forms were used for methodological quality assessment and data extraction. The following information was extracted from each eligible paper: study setting, design, population, number of participants and their demographic characteristics, type of physical symptom(s), data collection methods, outcomes of association of GP consultations for MUPS between parents and their children.

The association between GP consultations for MUPS between parents and children was defined and measured as the association between GP consultations for MUPS, history of treated MUPS, or medical diagnosis of functional somatic syndromes in parents and GP consultations for MUPS in children.

An important source of potential bias in any systematic review is bias due to limitations in the primary studies included within the systematic review (Sanderson et al., 2007). Therefore, examining the methodological quality of original studies is one of the key components in conducting systematic reviews (Mallen et al., 2006). Numerous tools have been used to examine the methodological quality of observational epidemiological studies, including checklists, checklists with summary judgement, and quality scales. Three systematic reviews identified and evaluated over a hundred quality scales and checklists used to assess the

methodological quality of epidemiological studies ((Sanderson et al., 2007, Mallen et al., 2006, Shamliyan et al., 2010). These systematic reviews have concluded that there is no consensus on a “gold standard” tool which can be used to appraise the methodological quality of observational studies, and that most existing tools lack validation.

In the current review, the methodological quality of included studies was appraised using a methodological quality assessment checklist for observational studies developed by Mallen and colleagues (2007). This checklist was developed using common items to assess the quality of observational studies in previously used quality checklists, including those used in published systematic reviews on musculoskeletal conditions (Mallen et al., 2007).

This checklist consists of 15 items covering internal and external validity (see box 4.2). Each study was scored according to its methodological quality using the 15 items checklist. Each item was scored positive (+) if it was satisfactorily presented, negative (–) if absent, or (na) if it was not applicable. Some items were not applicable as a function of study design, e.g. no losses or drop outs in cross-sectional studies and medical record reviews. The overall methodological quality of each study was rated as high if all or most of the items (>10) were fulfilled, moderate if some of the items (6 to 10) were fulfilled, and low if few or no items (0 to 5) were fulfilled. MS extracted data and assessed the methodological quality of all included studies. Two other reviewers (KD and CM) also extracted data and assessed the quality of included studies. All data were therefore independently extracted and the quality assessed by two different reviewers. Any disagreements were resolved by consensus or by the judgement of a third reviewer.

Box 4.2. Items used to assess the methodological quality of observational studies

A. Clearly defined study objective
B. Appropriate design for study question
C. Inclusion and exclusion criteria clear and appropriate
D. Representative sample (and comparison)
E. Sample size calculation presented
F. Appropriate selection of outcome
G. Appropriate measurement of outcome
H. Standardised collection of data
I. Adequate length of follow up for research question
J. Baseline participation >70% (all groups)
K. Losses and drop outs <20%
L. Adequate description of losses and completers
M. Appropriate analysis of outcomes measured
N. Numerical description of important outcomes given
O. Adjusted and unadjusted calculations provided (with confidence intervals if appropriate)

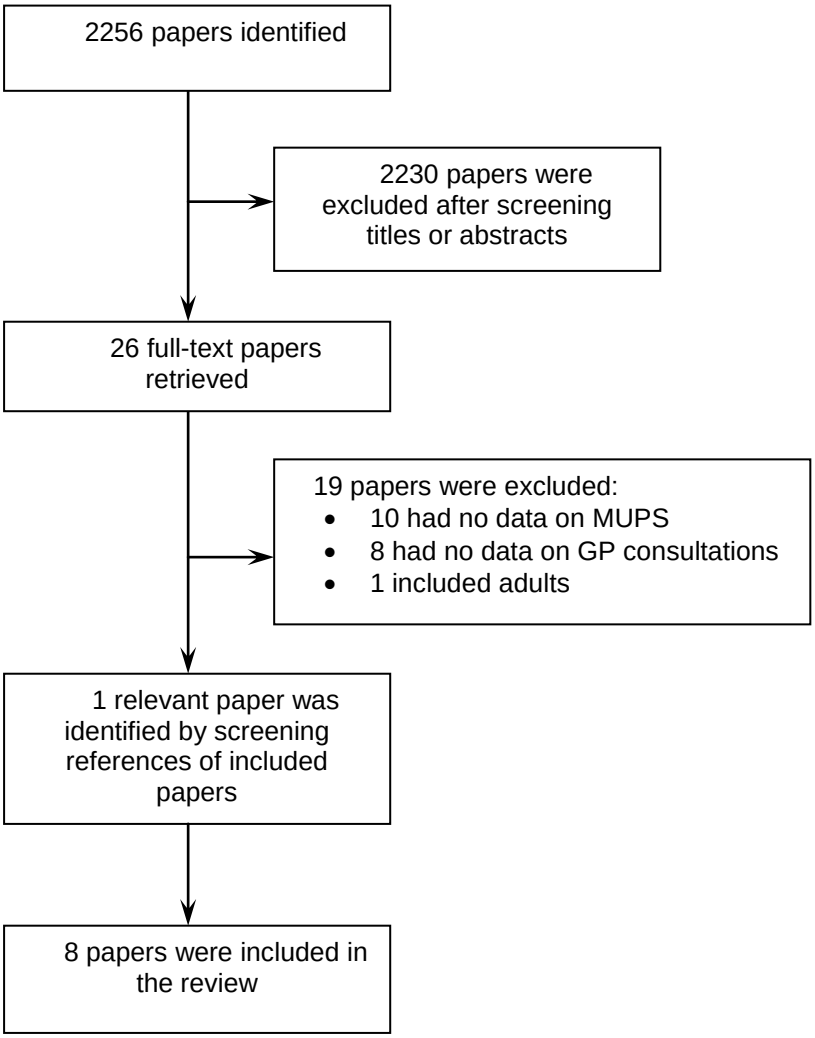
Source: Mallen et al. (2007, p.657)

4.4. Results

4.4.1. Studies identified

A total of 2256 papers were retrieved by searching the bibliographic databases (1106 MEDLINE, 745 EMBASE, 113 CINAHL and 292 PsycINFO). Of those, only eight papers were included in the review. Figure 4.1 presents more details about the results of systematic search and selection of studies.

Figure 4.1. Process of systematic search and selection of studies



4.4.2. Quality assessment

The overall methodological qualities of included studies were high. The following items were attained by all studies: clearly defined objective, appropriate study design, representative sample, appropriate selection of outcome, appropriate measurement of outcome, standardised data collection, and appropriate analysis of outcomes and numerical description of important outcomes

(see Table 4.1). Only two studies presented a sample size calculation. Losses and drop outs and adequate description of losses and completers items were not applicable to the majority of studies.

4.4.3. Characteristics of included studies

Study characteristics are presented in table 4.2. Included studies were published in English and were conducted in four different countries. Six studies were conducted in primary care and two studies identified children from schools. Studies were four cross-sectional surveys, three case-control studies and one retrospective cohort study. In four studies, the parent or the child reported information on MUPS and GP consultations, and the remaining studies used either medical records alone or medical records combined with self-reported data. The mean age of children ranged between 8.5 to 14 years. The mean proportion of females was 52% (range 49% to 60%).

Table 4.1. Results of quality assessment of included studies

	Quality assessment items															
Study	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**Overall Quality**
Balague 1995	+	+	+	+	-	+	+	+	+	+	na	na	+	+	+	High
Balague 1994	+	+	+	+	-	+	+	+	na	+	na	na	+	+	+	High
Campo 2007	+	+	+	+	-	+	+	+	+	na	na	na	+	+	+	High
Cardol 2006	+	+	+	+	+	+	+	+	+	na	na	na	+	+	+	High
Craig 2002	+	+	+	+	-	+	+	+	na	+	na	na	+	+	+	High
Levy 2004	+	+	+	+	-	+	+	+	+	-	na	na	+	+	+	High
Levy 2000	+	+	+	+	-	+	+	+	+	na	na	na	+	+	+	High
Little 2001	+	+	+	+	+	+	+	+	+	+	na	+	+	+	+	High

Na= not applicable; see Box 4.2 for detailed description of quality assessment items

4.4.4. Association between GP consultations for MUPS in parents and children

Table 4.3 presents the associations between GP consultations for MUPS in parents and children. Six studies found significant associations between GP consultations for MUPS, history of treated NSLBP, or IBS in parents and GP consultations for MUPS in children (Little et al., 2001, Craig et al., 2002, Levy et al., 2000, Levy et al., 2004, Cardol et al., 2006b, Balague et al., 1994); see table 4.3.

Four studies reported strength of associations as adjusted ORs with 95% CIs (Little et al., 2001, Campo et al., 2007, Levy et al., 2000, Balague et al., 1994), and two studies used adjusted *P*-values (Craig et al., 2002, Levy et al., 2004). One study did not report the strength of association, but stated it was not significant (Balague et al., 1995). One study reported the strength of association as the percentage of variation in consultation frequency attributed to shared family factors (Cardol et al., 2006b). One study (*n*= 456) found a significant association between self-reported GP consultations for MUPS in parents and children (adjusted OR 1.36, 95% CIs 1.10 to 1.70) (Little et al., 2001). Another study (*n*= 151) showed a significant association between somatisation disorder in mothers and maternal reports of GP consultations for MUPS in children (adjusted *p*-value <0.001) (Craig et al., 2002).

Three studies looked at IBS; one reported significant associations between IBS in parents and recorded GP consultations for GI symptoms in 1277 children (adjusted OR 2.2, 95% CIs 1.62 to 2.98) (Levy et al., 2000), and another between

IBS in mothers and recorded GP consultations for GI and non-GI symptoms in 641 children (Levy et al., 2004) (adjusted *P*-values 0.006 and 0.001, respectively). One study (*n*= 135) showed no significant association between history of IBS (adjusted OR 1.8, 95% CIs 0.6 to 6.1) and migraine (adjusted OR 1.4, 95% CIs 0.6 to 3.7) in mothers and maternal reports of GP consultations for FAP in children (Campo et al., 2007).

Two studies investigated the association between reported history of treated NSLBP in parents and history of NSLBP in children; one study (*n*= 1716) showed a significant association (adjusted OR 2.10, 95% CIs 1.56 to 2.83) (Balague et al., 1994) whereas the other study (*n*= 615) found no significant association (adjusted OR was reported as not significant) (Balague et al., 1995).

The final study (*n*= 65,671) reported the percentage of variance in similarity of recorded GP consultations among family members explained by family influence (Cardol et al., 2006b). For example, the variation in GP consultations by mothers and daughters that could be explained by family influence was 48% for headache and 35% for abdominal pain (see table 4.3).

Due to the high degree of study heterogeneity between studies, pooled estimates of the strength of associations were not performed.

Table 4.2. Characteristics of included studies

Study	Country	Setting	Study design	Child age (years)	Sex (% female)	Sample	MUPS	Data source
Balague 1995	Switzerland	School	Cross- sectional	12 to 17	52.5	615	NSLBP[b]	Self-report by children
Balague 1994	Switzerland	School	Cross- sectional	8 to 16	50.6	1716	NSLBP	Self-report by parents and children
Campo 2007	USA	PC[a]	Case-control	8 to 15	48.5	135	FAP[C]	Self-report by mothers
Cardol 2006	The Netherlands	PC	Cohort	1 to 12	60	65671	MMUPS[d]	Medical records review
Craig 2002	UK	PC	Cross sectional	4 to 8	52	151	MMUPS	Medical records review (mothers) & mothers reported on the child GP consultation for MUPS
Levy 2004	USA	PC	Case-control	8 to 15	51	641	MMUPS	Medical records review (mothers and children) & mothers reported on the child MUPS
Levy 2000	USA	PC	Case-control	3 to 14	49	1277	GI[e]	Medical records review (parents and children)
Little 2001	UK	PC	Cross sectional	<16	50	456	MMUPS	Self-report (parents)

[a]Primary care; [b]Non-specific Low-back pain; [C]Functional abdominal pain; [d]Multiple medically unexplained physical symptoms; [e]Gastrointestinal

Table 4.3. Associations between GP consultations for MUPS in parents and children

Study	Time period	Summary of association	Factors adjusted for in multivariable analyses	Strength of association
Levy 2000	1 year	Children of parents with IBS[a] had significantly more GP consultations for GI[b] symptoms compared to control children and parents	Child age and gender, parent age and gender, parental health care use for non-GI disorders	Crude OR[c] not reported, adjusted OR 2.2; 95% CIs[d] 1.62, 2.98
Little 2001	1 year	GP consultations for MUPS[e] in high attending children were significantly associated with parental GP consultations for MUPS	Child gender, parental perceived health of the child, willing to tolerate child symptoms, health anxiety, and council house tenancy	Crude OR not reported, adjusted OR 1.36; 95% CIs 1.10, 1.70
Balague 1994	Life time	Children with parental history of treated NSLBP[f] were more likely to report a history of NSLBP themselves	Child age, gender, competitive sports activity, TV watched (hours/week)	Crude OR 1.87, 95% CIs 1.42, 2.48; adjusted OR 2.10, 95% CIs 1.56, 2.83
Balague 1995	Life time	No significant association was found between parental reported history of treated NSLBP and children's lifetime history of NSLBP	Child gender, age, walk time, sports activity, negative affect, positive affect, and siblings' NSLBP	Crude OR 1.09, 95% CIs were not reported; adjusted OR was not reported
Campo 2007	Life time	No significant association was found between child GP consultations for FAP[g] and maternal MUPS	Maternal age, maternal anxiety and depressive disorders, and family intact (child lives with biological parents)	For IBS: crude OR 3.9, 95% CIs 1.5, 10.3; adjusted OR 1.8, 95% CIs 0.6, 6.1. For migraine: crude OR 2.4, 95% CIs 1.1, 5.3; adjusted OR 1.4, 95% CIs 0.6, 3.7

Study	Time period	Summary of association	Factors adjusted for in multivariable analyses	Strength of association
Craig 2002	3 months	Children of somatising mothers had significantly more GP consultations for MUPS compared to children of control mothers	Child age and gender, child emotional or behavioural problems, mother's exposure to adversity in her own childhood, and maternal psychiatric disorders	Adjusted *P*[h]= <0.001
Levy 2004	3 years	Children of mothers with IBS had significantly more GP consultations for GI and non-GI MUPS than controls	Child age and gender, child sense of competence, child coping style, child psychological symptoms, and maternal stress and psychological symptoms	For GI symptoms, crude *P*= 0.005 and adjusted *P*= 0.006 For non-GI symptoms, crude and adjusted *P*= 0.001
Cardol 2006	1 year	There was an association in GP consultation frequency for headache and abdominal pain between children and their parents compared to other families in which children consulted for physical trauma or chronic disease	Child age and gender and GP practice	Percentage of variation in GP consultation frequency attributed to shared family factors (95% CIs)

Family members	Headache	Abdominal pain	Minor ailments
Mother-son	20.2 (16.4, 24.1)	34.1 (31.0, 37.1)	19 (18.0, 20.0)
Mother-daughter	48.4 (44.5, 52.3)	34.7 (31.7, 37.7)	23.2 (22.1, 24.3)
Father-son	4.7 (2.7, 7.2)	17.1 (14.4, 19.8)	8.8 (8.0, 9.7)
Father-daughter	14.4 (11.1, 18.1)	6.9 (5.1, 8.9)	4.9 (4.3, 5.6)

[a]Irritable Bowel Syndrome; [b]Gastrointestinal; [c]Odds ratio; [d]Confidence intervals; [e]Medically unexplained physical symptoms; [f]Non-specific Low back pain; [g]Functional Abdominal Pain; [h]*P*-value

4.5. Discussion

4.5.1. Summary of main findings

This review provides evidence that GP consultations for MUPS in parents are associated with GP consultations for MUPS in their children. The review included eight studies, of which six found significant associations between GP consultations for MUPS in parents and children. Differences between studies in study design, settings, data collection methods, ages and numbers of included children, and types of included MUPS may partly explain the lack of association found in two studies. For example, these two studies examined the association between the lifetime prevalence of reported NSLBP in children and history of treated NSLBP in parents and reported mixed findings. In the first study (Balague et al., 1994), schoolchildren reported information on their lifetime prevalence of NSLBP was well as the history of treated NSLBP in parents, while in the other study (Balague et al., 1995), both parents and children reported information on history of their NSLBP. Therefore, possible lack of children's knowledge of their parents' history of treated NSLBP or recall bias may partially explain the contradictory findings of these two studies.

The mechanisms underlying the association of GP consultations for MUPS between parents and children are not fully clear. However, there is some evidence that genetic effects (Larsson et al., 1995, Morris-Yates et al., 1998), shared environmental factors (Huurre et al., 2006, Troxel & Matthews, 2004), and childhood social learning of illness behaviour (Craig et al., 2002, Levy et al., 2007,

Cardol et al., 2007, Levy et al., 2000) might explain this association. Although the majority of studies controlled for some possible confounding factors, it has been suggested that parental decision to seek healthcare for their children may reflect parental health attitudes, health beliefs and consulting behaviour rather than the child healthcare needs (Campo et al., 2007, Levy et al., 2000, Levy et al., 2004). Therefore, the association of GP consultations for MUPS in parents and children may be explained by parental biased perception of symptoms in children or parental concentration on the symptoms they have themselves. For example, in one study, children with GI symptoms were interviewed independently of their mothers with IBS, and found that the difference between children of cases and controls was greater when the mothers reported on symptoms in children compared to children's reports on their own symptoms (Levy et al., 2004). Also, the observed association of GP consultations for MUPS between parents and children may perhaps just reflect patterns of GP consultations more generally.

4.5.2. Comparison with existing literature

As far as the author is aware, this is the first systematic review to summarise the research evidence on the association between GP consultations for MUPS in parents and their children. The findings from this review are in agreement with findings of other studies that specifically focused on the association of self-reported MUPS (without including GP consultations data) between parents and children, which showed mixed results (Kashikar-Zuck et al., 2008, Saunders et al., 2007, Jones et al., 2004, Huang et al., 2000, Devanarayana et al., 2008, Boey & Goh, 2001b). For example, two studies reported significant associations for self-

reported history of FAP between parents and children (Devanarayana et al., 2008, Boey & Goh, 2001b), whereas this association was found not significant in another study (Huang et al., 2000).

4.5.3. Implications for clinical practice

The potential impact of parental GP consultations for MUPS on the health and GP consultations behaviour of their children has implications for primary care. It is important that GPs be aware of this link, as such insights might direct the GP toward alternative management approaches. For example, one study found that cognitive behaviour therapy (CBT) targeting children's coping responses to FAP and parents' responses to pain in their children was associated with significant reduction in pain and MUPS severity in CBT group children than control group (Levy et al., 2010). Another study showed that CBT for children with persistent MUPS and anxiety was associated with significant improvements in anxiety symptoms and reduction in pain severity and discomfort due to GI symptoms as compared to controls (Warner et al., 2011).

4.5.4. Strengths and limitations of this review

This review included only eight studies. This was despite a comprehensive search covering several electronic bibliographic databases. The citations for all included studies were searched and did not identify any further relevant studies. Only one relevant paper was identified through searching the references lists of included studies. The search did not address all sources of grey literature.

However, local experts were contacted to identify any relevant studies, and search was not restricted to English-language publications. Also, no studies were excluded from the review on the basis of quality assessment.

In addition to the high degree of heterogeneity among included studies, there are some limitations that should be considered when interpreting the results of this review. First, the majority of included studies relied on self-reported data, which is prone to recall bias. However, two studies examined agreement between self-reported and documented consultation for MUPS, and they showed a good level of agreement (Little et al., 2001, Craig et al., 2002). Second, four studies used self-reported data on history of IBS or treated MUPS rather than patterns of GP consultations for these conditions. However, it is reasonable to suggest that those parents had to consult a medical practitioner to receive treatment and diagnosis for those conditions. Third, due to the small number of included studies, assessment for publication bias was not performed. Therefore, the potential for publication bias remains unknown. Fourth, although all studies were generally of high methodological quality, only two studies reported a priori calculation of sample size. Last, four studies were cross-sectional and are therefore unable to disentangle the direction of associations.

4.5.5. Conclusion

This chapter has presented the findings of a systematic review which provide some evidence of an association between GP consultations for MUPS in parents and children. GPs need to be aware of this link which has implications for the management and prevention of MUPS among children in primary care. There are

limited numbers of studies that have investigated the association of GP consultations for MUPS between parents and their children. Further longitudinal research, without relying on retrospective recall of MUPS experience, is needed to further investigate the association between GP consultations for MUPS among parents and children. Further studies may wish to investigate this association by focusing on the whole spectrum of MUPS including different age groups of children. Such research may provide more precise measures of impact of parental MUPS on the health and GP consultation behaviour of their children, which has implications for the management and prevention of MUPS.

Chapter 5. General study methods

5.1. Introduction

Before addressing the remaining objectives for this thesis, the operational definitions and terms used in this research will be presented and discussed. This chapter introduces the CiPCA database and presents the methods used to identify household members in the CiPCA GP practices. Then, an operational definition for a family, the process of identifying family members for index children included in this research, and characteristics of households in the CiPCA practices are presented. The next sections provide definitions for define a GP consultation, MUPS, GP consultations for MUPS, and discuss the methods used to identify GP consultations for MUPS. Additionally, an overview of the English indices of multiple deprivation and an operational definition of frequent GP consultation in children are given.

5.2. Household member identification in the CiPCA database

5.2.1. The CiPCA database

The CiPCA database is a high quality, anonymised, validated database, which contains all routinely recorded morbidity data from consultations occurring at 12 general practices in North Staffordshire since 1997 (IPCHS, 2012). These general practices are part of the Keele GP Research Partnership, which has regular cycles of training, assessment and feedback with respect to quality of their recorded

morbidity coding (Porcheret et al., 2004). Data from CiPCA on prevalence rates of the annual persons consulting for musculoskeletal conditions were comparable to data from larger national general practice databases (Jordan et al., 2007).

The CiPCA database is held at the Arthritis Research UK Primary Care Centre at Keele University, and managed and audited by the informatics team within the centre (IPCHS, 2012).

There are other data archives within the centre that are related to the CiPCA database. These datasets include

- Prescriptions in Primary Care Archive (PiPCA)
- Referrals in Primary Care Archive (RiPCA)
- Medical Certificates in Primary Care Archive (MiPCA)
- Demographic and Deprivation Data in Primary Care Archive (DiPCA)

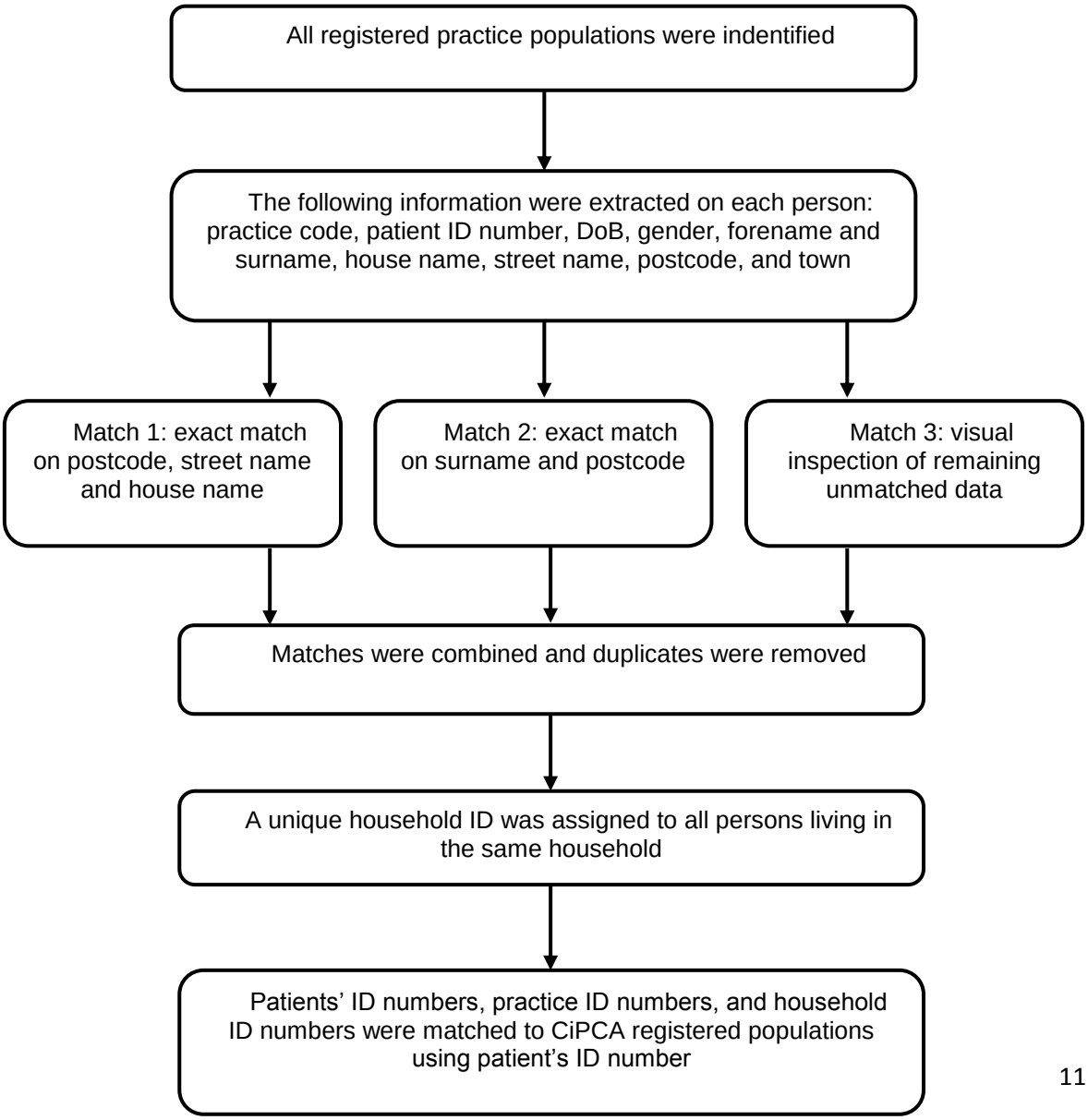
Appendix 2 presents the data available within the CiPCA and DiPCA databases.

5.2.2. Method of household members' identification in CiPCA practices

When the author started this PhD project, CiPCA database didn't include a unique household identification (ID) number. A unique household ID number based on address details from GP practices registered populations helps to identify all persons living in a household and registered with the same GP practice. A unique household ID for all CiPCA practices registered populations was needed to identify family members of children included in this research.

A member from the informatics team in the Centre and the author visited 12 CiPCA GP practices and used their computerised lists of all registered populations to assign a unique household ID to all persons registered with these practices. Figure 5.1 illustrates the process of household members' identification in the 12 CiPCA practices. This process was carried out at the practices due to ethical constraints. The author obtained permission to enter the practices and access lists of GP practices registered populations from NHS North Staffordshire and NHS Stoke on Trent.

Figure 5.1. Process of household members' identification in CiPCA practices



To identify all persons registered as living in the same household, we extracted the following information on all persons registered with each GP practice: practice code (unique code identifying each practice), person's unique practice ID number, date of birth (DoB), gender, forename, surname, house name, street name, postcode and town name. Then, this information was exported to Excel. Household members were identified by ordering the extracted information using different criteria and matches, and then comparing the data in one row with the data in the row above. Three individual matches were carried out to identify each household's members:

- Match one: exact match on address by sorting the dataset by postcode, street name and house name.
- Match two: exact match on surname and postcode by sorting the dataset by surname and postcode.
- Match three: exact match based on visual inspection of all the remaining data to identify household's members that were not identified through match one and match two.

Some members of households were not identified initially due to spelling errors, using no space or double space when recording persons' addresses by practice staff, or using different abbreviations, such as rd for road, st for street, cl for close, etc. After correcting all spelling errors and standardising street name by replacing abbreviated street name by full street name, match one was repeated to identify the remaining household members. Once all persons registered to be living in a household were identified, a unique household ID was assigned to all persons in

that household. All unique practice ID, unique personal ID and household ID numbers for all practices' registered populations were then extracted and uploaded to CiPCA database. Thus, each person from these 12 CiPCA practices has a household ID that can be used to identify all other household members. All information used to identify households' members was erased before leaving each practice.

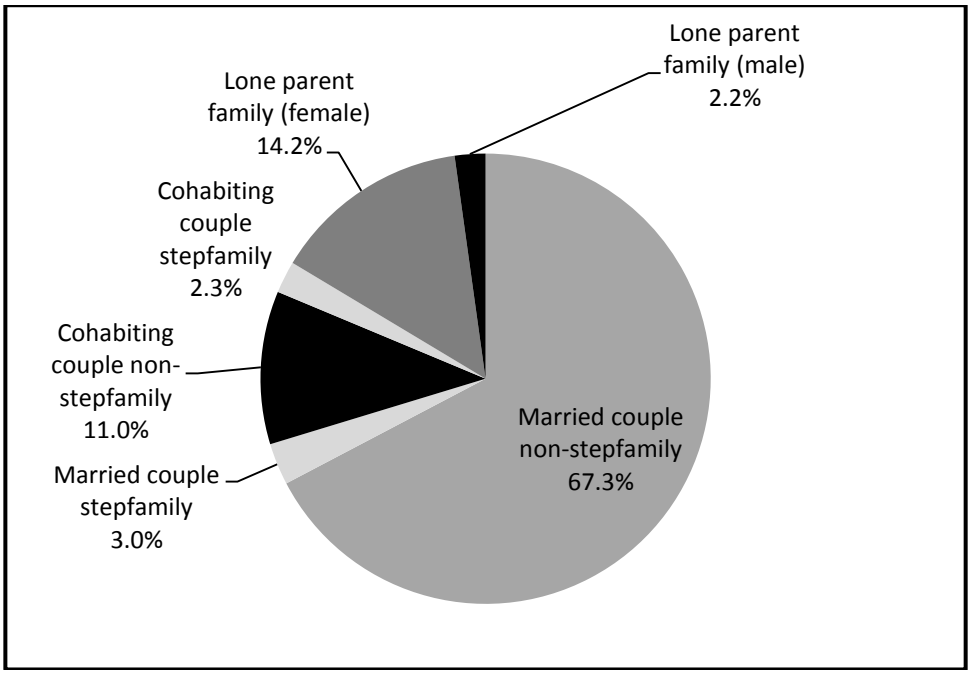
5.3. Definition of family

The term 'family' is broad as families can take many shapes in a wide variety of settings and, therefore, there is no universal definition of the family. Traditionally, the 'family' is defined as "*a fundamental social group in society typically consisting of one or two parents and their children living together under one roof*" (The American Heritage Dictionary of the English Language, 2012). Currently, many families consist of a number of non-traditional structures such as stepfamilies, cohabiting parents, single parents, couples living together, civil partnerships, grandparent-led families, foster families, and gay or lesbian couples. The Office for National Statistics in the UK (ONS) defines family as *"a married or cohabiting couple, with or without their never married child or children (of any age), including couples with no children and lone parents with their never-married child or children. A family could also consist of a grandparent or grandparents with grandchild or grandchildren if the parents of the grandchild or grandchildren are not usually resident in the household."* (ONS, 2007b).

In the UK, the traditional family structure has shifted significantly over the last few decades (Jenkins et al., 2009). A number of changes in demographic trends,

such as the decline and delay of marriage and childbearing, the rise in divorce rate, the rise in birth outside marriage and the significant increase in cohabitation, have resulted in new forms of family composition (Jenkins et al., 2009). Figure 5.2 presents the proportion of families in the UK by type in 2007 (ONS, 2007b).

Figure 5.2. Proportion of UK families by type in 2007

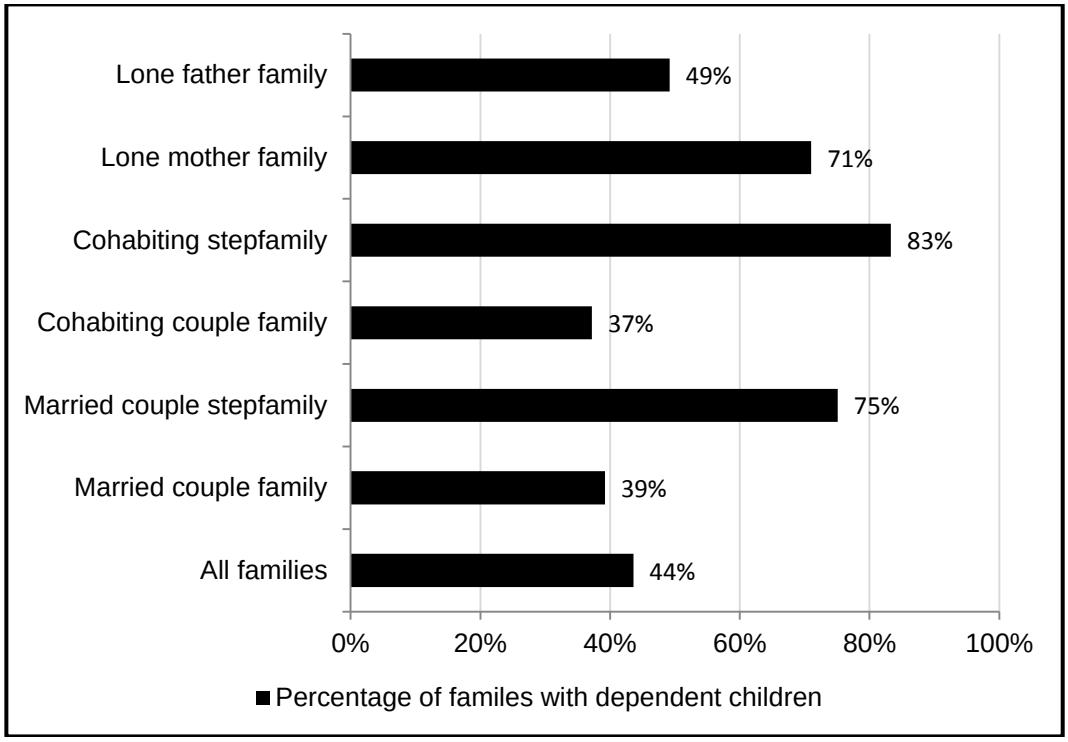


Source: ONS (2007)

Currently, many children in the UK grow up in single-parent and stepfamily households. Figure 5.3 shows a distribution of families in the UK by family type and presence of children (ONS, 2007b, ONS, 2007b). Therefore, GP practice registration data does not necessarily provide accurate information on family members such as biological parents and siblings of registered children. In situations where no family data are available for research purposes such as GP practice registered populations, household data can provide meaningful insights

about family or household members (ONS, 2007a). However, identifying family or household members and establishing family structure (identifying parents and their children) based on lists of GP registered populations can be a complex task.

Figure 5.3. Families in UK by family type and presence of children, 2001



Source: ONS (2007)

The ONS defines a household as a person who lives alone, or a group of people who have the same address as their only or main residence and with common housekeeping (ONS, 2007a). This definition excludes those people living in communal establishments (e.g. hospitals, hotels, etc). Therefore, a household may contain more than one family, or may contain people living in the household who are not family members, such as friends, relatives, and children living in non-

family households. However, data from ONS shows that, in 2006, only 1% of households in the UK contained more than one family (ONS, 2007a). Only 2 percent of households in the UK contain 6 or more persons (ONS, 2007b). In the UK, a very small minority of children (about 1 per cent) were living in non-family households in 2001(ONS, 2007a). Also, in 2009, 84% of live births in England and Wales were registered by two parents, whether married or cohabited, living at the same address (ONS, 2007a). Additionally, family members, especially parents and their children, usually register with the same GP practice (Cardol et al., 2006b). Thus, list of GP registered populations may be a useful source for identifying family or household members among these populations.

For the purpose of this thesis, a family was defined as at least one adult age 17 or more and at least one child who live together in the same household and being registered with the same GP practice (Cardol et al., 2007). A child was defined as a person aged 16 years and under.

5.3.1. Identifying family members for index children

In this thesis, only one child per household was included. If the household had more than one child, one index child was chosen at random. The randomisation was done by using random number generator to assign a unique number to each child in the household. The children's unique numbers were then ordered in ascending order and the first child from each household was selected as the index child.

The process then involved identifying family members for index children, including parents and siblings. All GP consultations and records from the 12 CiPCA practices between December 2005 and December 2009 were used to identify potential family members for index children. Identifying family members of index children was based on data from ONS in UK and previous literature as follows:

Unique household IDs for index children were used to identify all other persons registered as being living in those households as selected children. Data from ONS on live births by age group of mothers and fathers in England and Wales in 2010 was used to identify parents for index children (ONS, 2010b). According to ONS, about 99.3% and 99.6% of babies born in England and Wales in 2010 were most likely to have a mother aged 17 to 45 years and a father aged 20 to 54 years at the birth of the child, respectively (ONS, 2010b). Therefore, a mother was defined as a female aged 17 to 45 years at the birth of the index child, and has the exact household ID as the index child. A more precise way to identify mothers of index children is to match mothers' birth codes to children's dates of birth. This method was used by McKeever and colleagues to identify mothers of selected children in a birth cohort study of incidence of allergic disease using the West Midlands general practice research database (McKeever et al., 2001). However, birth codes are not available in the CiPCA database. A father was defined as a male aged 20 to 54 years at the birth of the index child, and has the exact household ID as the index child. In the case where multiple potential mothers or fathers were present for index children, the index child and his/her household members were excluded to avoid errors in selecting potential parents for index

children. All households with more than 12 members (McKeever et al., 2001), or less than two members, or without children aged 16 and under were excluded.

Younger and older siblings for index children were identified using same methods used in the McKeever study (McKeever et al., 2001). Younger siblings for index children were defined as persons from the same household and born after the index child (McKeever et al., 2001). Older siblings were defined as persons from the same household and aged 16 or less at the birth of the index child (McKeever et al., 2001).

5.3.2. Characteristics of households for index children

Figure 5.4 illustrates the process of selection of index children for whom family members were identified using the methods discussed above in section 5.2.1. Initially, 15661 households containing data on 56017 members were identified. Households with no children (or with no children born between 1.1.1993 and 31.12.2007 (*n*= 3712), households with more than 12 members (*n*=15), and households with only one member (*n*=105) were excluded at this stage. Of the remaining 11829 households with children, a further 1369 households were excluded: 982 households had multiple potential parents and 387 households had no potential parents. For example, the majority of these households contained older children aged 14 to 16 years living with young adults in their twenties. Some households contained children living with young adults, where the age differences between the adults and the children were less than 17 years, and, therefore those adults did not qualify to be included as parents for those children. A total of 10460 households met the definition for family and were included.

Figure 5.4. Process of selection of index children

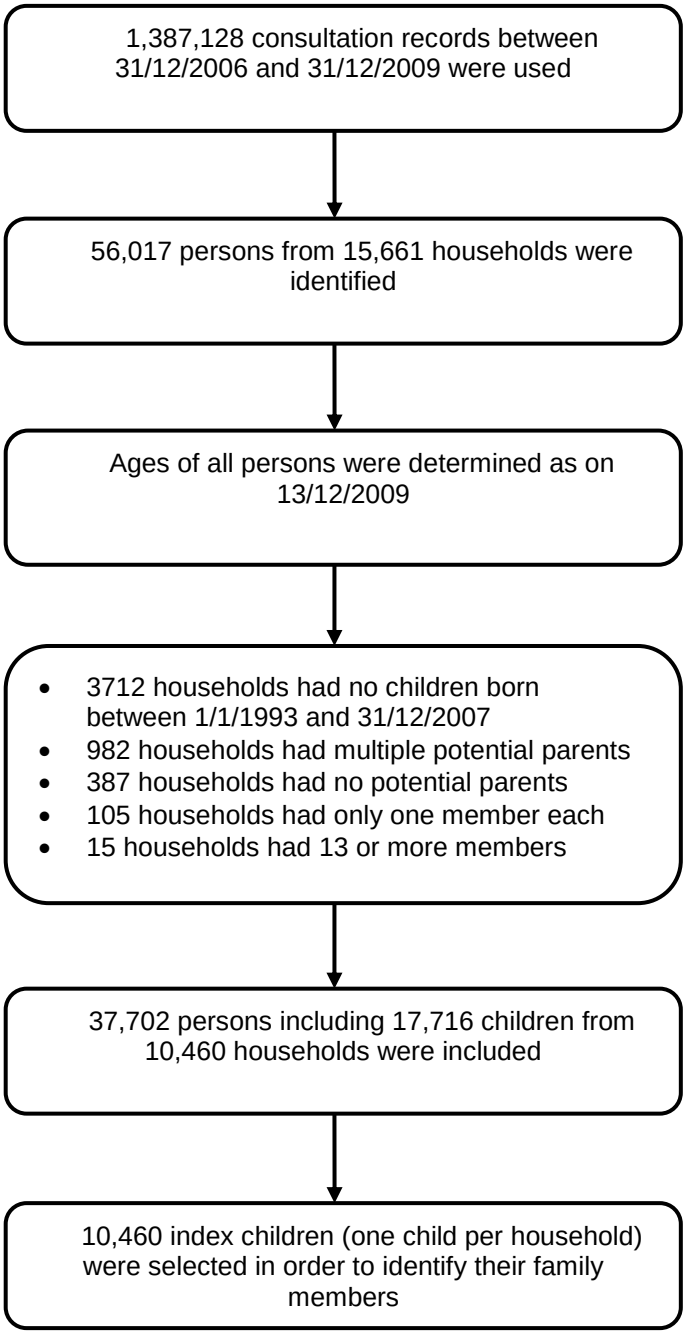


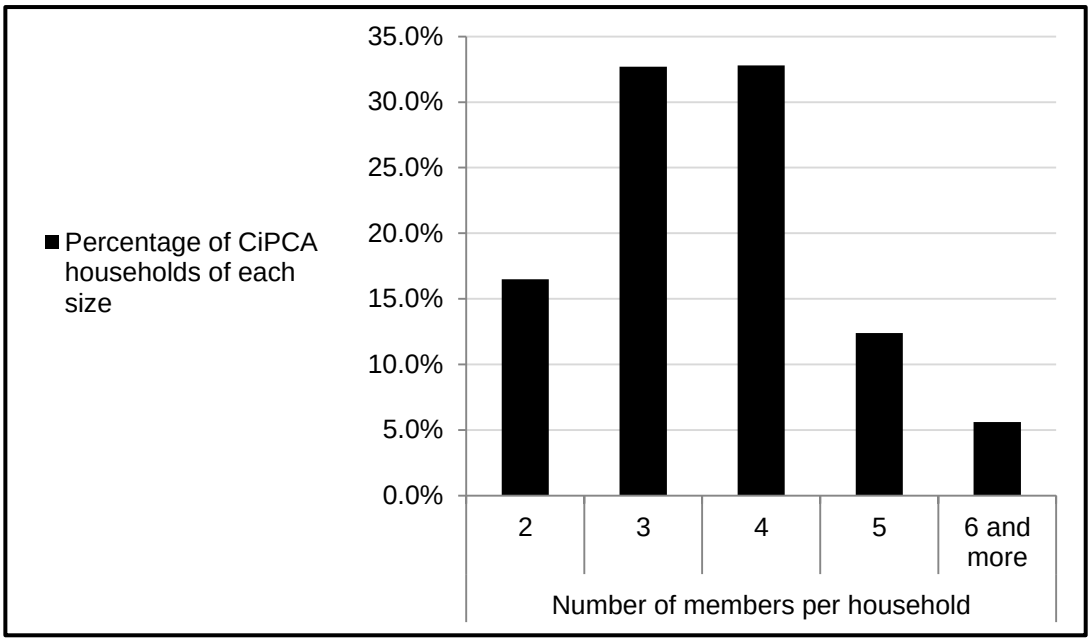
Table 5.1 presents the characteristics of CiPCA households, which included 10460 households that contained 10460 index children, 16088 parents, 9885 siblings, and 1269 other household members (potentially grandparents).

Table 5.1. Characteristics of included households

Characteristic	Number, mean or %
Households	
Number	10460
Total number of households' members	37702
Mean number of household members (SD; range)	3.6 (1.16; 2-12)
Mean number of children in household (SD; range)	1.69 (0.84; 1-8)
Percentage of households with on child	49.0
Percentage of households with two children	37.1
Percentage of households with three or more children	13.9
Total number of households with data on both parents (%)	5628 (53.8)
Total number of households with data on mother only (%)	4452 (42.6)
Total number of households with data on father only (%)	380 (3.6)
Children	
Number	10460
Mean age on 31.12.2009 (SD; range)	9.0 (4.52; 2-16)
Girls number (%)	5130 (49.0)
Parents	
Mean age of mothers 31.12.2009 (SD; range)	38.0 (7.19; 19-61)
Mean age of fathers 31.12.2009 (SD; range)	40.3 (7.5; 19-66)
Siblings	
Mean number of siblings in household for selected children (SD; range)	0.95 (0.94; 0-8)

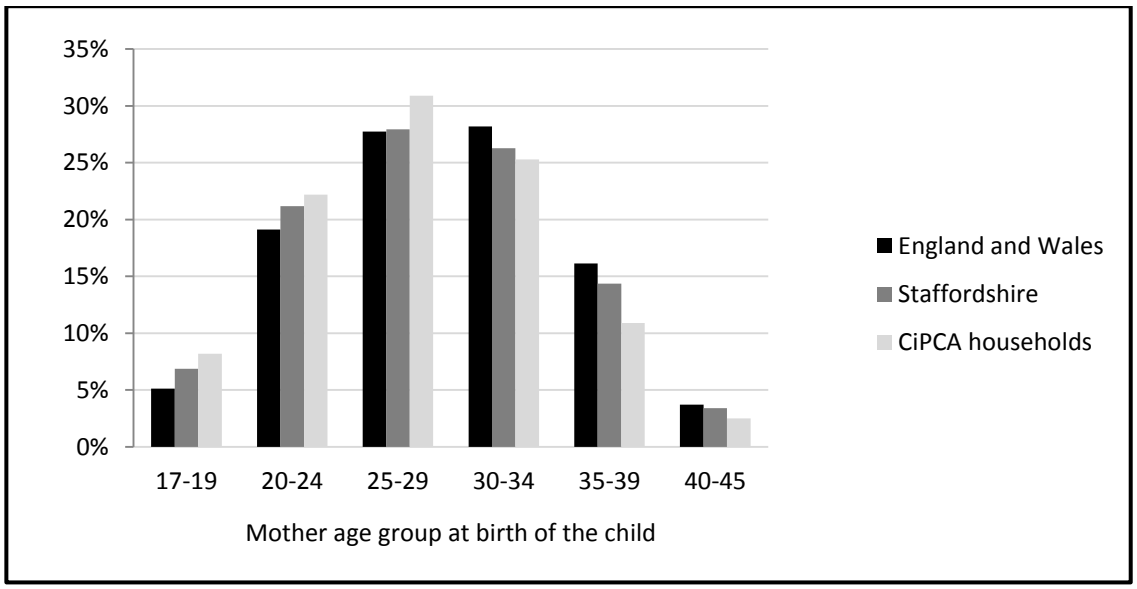
The mean age of the children was 9.0 years, and the mean age for mothers and fathers were 38.0 years and 40.3 years, respectively. The mean number of children for selected households was 1.7, which is identical to the mean number of dependent children (1.7) for all families in the UK based on data from the General Household Survey (GHS) in 2007 (ONS, 2007b). The mean number of household members was 3.6; 94.4% of selected households had less than 6 members. Figure 5.5 summarises the total members in household by percentage of households of each size.

Figure 5.5. Total members in CiPCA households



To explore the validity of methods used to identify family members for index children in the selected CiPCA households, a number of comparisons were made between characteristics of CiPCA households and characteristics of all family households in the UK or local areas. As shown in figure 5.6, data on live births by age group of mother at birth of the baby in England and Wales and Staffordshire area in 2010 (ONS, 2010a) were similar to age group of mothers at the date of birth of selected children in CiPCA households. For example, 55.9% of babies born in England and Wales and 54.2% of babies born in Staffordshire in 2010 were most likely to have a mother aged 25 to 34. In CiPCA households, 56.2% of selected children had a mother aged 25 to 34. Similarly, proportions of babies born in England and Wales and Staffordshire in 2010 for mothers aged under 25 or aged 35 and over were comparable to that of CiPCA population (see figure 5.6).

Figure 5.6. Percentage of live births by age group of mother in England and Wales and Staffordshire region, and age group of mothers at birth of index children in CiPCA households



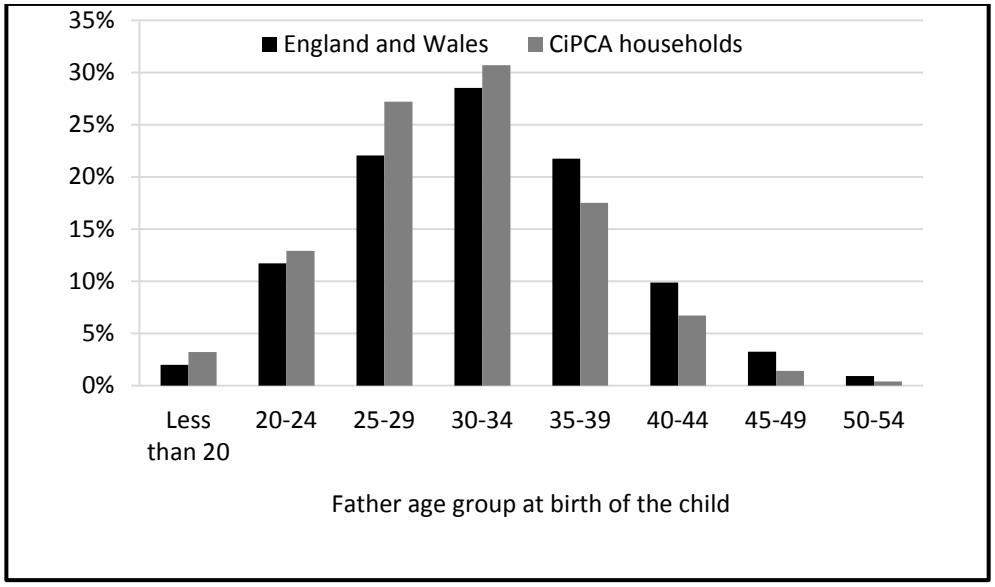
Source ONS (2010)

Data on live births by age group of father at the birth of the baby in England and Wales (data on age group of fathers in Staffordshire area was not reported by ONS) in 2010 was similar to age group of fathers at the date of birth of index children in CiPCA households (ONS, 2010b). Approximately 94% of babies born in England and Wales in 2010 and 95% of index children in CiPCA households had a father in the age group between 20 and 44 years, respectively (see figure 5.7).

Also, percentages of number of children in CiPCA households were similar to percentages of number of children in all family households in the UK. Figure 5.8 shows the percentages of number of children in all CiPCA households compared to percentages of number of children in all families in UK based on data from Labour Force Survey in 2010 and data from Family Resources Survey in 2009 in UK and West Midlands region (Department of Work and Pensions, 2009).

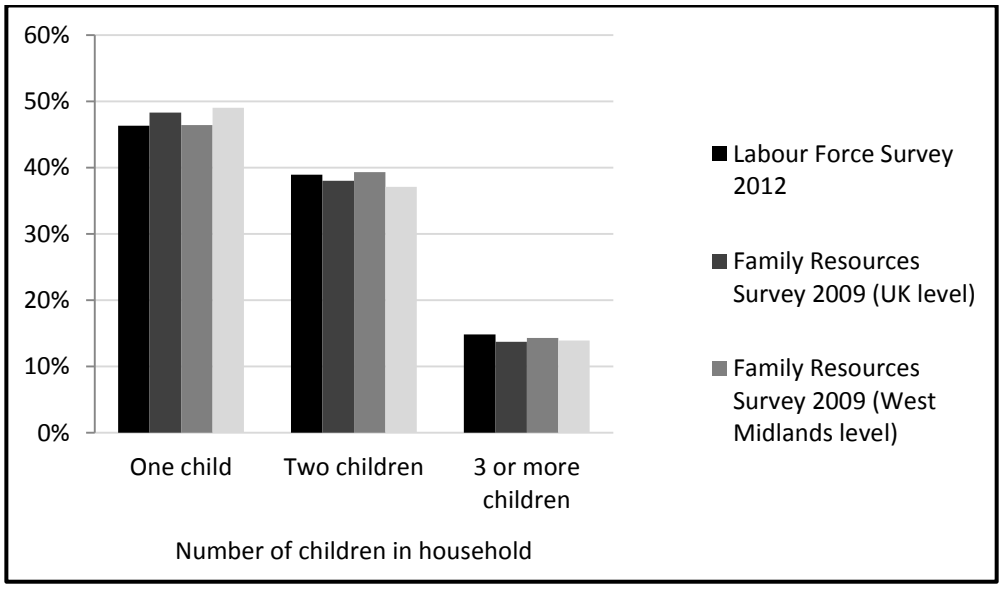
Additionally, the age group of the youngest child in the CiPCA households were similar to those in all families in the UK based on data from the General Household Survey (GHS) in 2007, see figure 5.9 (ONS, 2007b).

Figure 5.7. Percentage of live births by age group of father in England and Wales & age group of father at birth of index children in CiPCA households



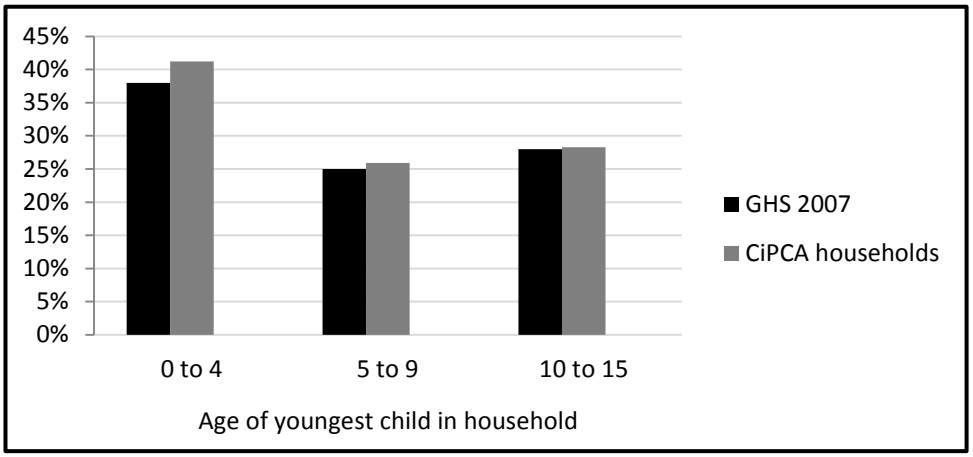
Source ONS (2010)

Figure 5.8. Percentage of number of children in household in UK and CiPCA households



Source: Department of work and pension (2009); ONS (2012)

Figure 5.9. Percentage of age group for youngest child in the family in UK and CiPCA households



Source ONS (2007)

5.4. Definition of GP consultation

A GP consultation was defined as a recorded contact between a GP and a patient which occurred at the GP surgery, by home visit or by telephone (Foster et al., 2006). The included 12 CiPCA GP practices use the Egton Medical Information System (EMIS) computer system to electronically manage and store patients' primary care medical records. In EMIS, it is recommended that the GPs use the "Consultation Mode" to record consultations with patients in the surgery, on the phone, or following a home visit. The "Consultation Mode" records a date, location and doctor identity (e.g. GP, GP registrar, or Locum GP) each time it is opened for a patient. When the GP enter data into patients medical records outside of consultations, such as checking laboratory results, the "Medical Records" option in EMIS is used and entered data are not recorded as consultations.

Four data items were used to identify all consultations that meet the definition for GP consultation. These four data items included: the date of consultation, the

patient ID, the location of consultation (surgery, telephone, or home visit), and the GP type (e.g.GP, GP principal, GP salaried, GP locum, GP registrar, GP trainee). Consultations were only included in analysis if these four data items were recorded for each consultation and met the definition for GP consultation. All clinical activity records that occurred outside of consultations such as electronic laboratory results, repeat prescriptions, and administrative records were not counted as GP consultations.

5.5. Definition of MUPS

As discussed in section 2.2., MUPS are defined as physical symptoms that lead the patient to seek medical help, and after clinical assessment, do not seem to be explained by a clearly defined cause or a diagnosis of a defined medical disease (Nimnuan et al., 2001a, Melville, 1987). MUPS that were included in this thesis are listed in box 5.1. This list includes MUPS that were used in the Children's Somatization Inventory, which includes MUPS from the diagnostic criteria for DSM-III-R Somatization Disorder and Somatisation factor of the Hopkins Symptom Checklist (Walker et al., 2009). This list includes 33 MUPS from the diagnostic criteria for DSM-III-R Somatization Disorder (American Psychiatric Association, 1987) and nine MUPS from the somatization factor of the Hopkins Symptom Checklist (HSCL) (Derogatis et al., 1974). These MUPS were included in previous studies of Children's Somatization Inventory (Garber et al., 1991, Walker et al., 2009, Vila et al., 2009, Meesters et al., 2003) and other epidemiological studies investigating MUPS in children and adolescents (Eminson et al., 1996, Rask et al., 2009). This list includes the most prevalent MUPS reported in general populations

(Liu et al., 1997, Kroenke & Price, 1993), outpatient clinics (Kroenke et al., 1990), and primary care settings (Kroenke & Jackson, 1998, Khan et al., 2003, Kroenke et al., 2002, Simon et al., 1996).

Three sexual symptoms (sexual indifference, painful sexual intercourse, and erectile or ejaculatory dysfunction) from diagnostic criteria for DSM-III-R Somatization Disorder were excluded from analysis for children. Therefore, this list includes 39 MUPS for children and 42 MUPS for parents (shown in box 5.1). The individual MUPS are grouped into five body symptom groups (Musculoskeletal, Cardiopulmonary, Gastrointestinal, Genitourinary, Neurological), plus one general symptom group including fatigue.

5.5.1. Identification of GP consultations for MUPS

GP consultations for MUPS were identified using a list of Read codes corresponding to MUPS listed in box 5.1. The Read codes are a hierarchy of morbidity, symptoms and process codes that are used to record all electronic morbidity data in General Practice in the UK (Chisholm, 1990). For example, the Read code ‘XE0as’ is used to record Irritable Bowel Syndrome. The usage of Read codes to code clinical data onto GP computer clinical system is encouraged. In 2006, 97% of all GP consultations that occurred at CiPCA GP practices were given a morbidity Read code (Jordan et al., 2010). The Read coding system cover many topics that clinicians use to record on their clinical system, which include occupations, signs and symptoms, investigations, diagnoses, operations, drugs, therapies, and general administrative information. Read codes are cross-referenced to ICD-10, Classification of Interventions and Procedures (OPCS), the

British National Formulary (BNF) and the Anatomical Therapeutic Chemical (ATC) Classification System for drugs.

Box 5.1. List of included MUPS

Musculoskeletal symptoms
Pain in extremities
Back pain
Arthralgia (joint pain)
Muscles soreness

Gastrointestinal symptoms
Vomiting
Abdominal pain
Nausea
Abdominal bloating
Diarrhoea
Constipation
Multiple food intolerance
Globus (lump in the throat)
Dysphagia (difficulty swallowing)

Cardiopulmonary symptoms
Palpitations
Chest pain
Hyperventilation or Dyspnoea
Hot or cold spells (sweat)

Urogenital symptoms
Pain during urination
Difficulty urinating (Dysuria)
Burning sensation in sexual organs or rectum
Dysmenorrhoea (painful menstruation)
Metrorrhagia (irregular menstrual periods)
Menorrhagia (heavy menstrual bleeding)
Sexual indifference (decreased libido)*
Dyspareunia (pain during intercourse)*
Impotence (erectile or ejaculatory dysfunction)*

Neurologic symptoms
Dizziness
Fainting (syncope) or loss of consciousness
Transient Amnesia (Loss of memory)
Transient Aphonia (loss of voice)
Transient Deafness
Diplopia (double vision)
Blurred vision
Transient blindness
Seizure or convulsion
Transient Ataxia (trouble walking)
Transient Paresis (paralysis)
Headache
Parasthesia (numbness or tingling sensation)
Weakness in parts of the body
Heavy feelings in arms or legs

General symptoms
Fatigue

*Symptoms were excluded from analysis for children

Read codes are structured into different chapters, which include 0-9 codes for processes of care, A-Z (uppercase) codes for diagnosis, and a-z (lowercase) codes for drugs (see appendix 3). Read codes have a hierarchical structure

containing 5 levels of detail in the current 5 character version (5 byte) of the codes. Table 5.2 shows an example of the Read code hierarchy for 5 bytes codes.

Table 5.2. Example of READ code Hierarchy for 5 bytes codes

Read Code	Clinical term
H….	Respiratory system diseases
H0…	Acute respiratory infections
H03..	Acute tonsillitis
H035.	Acute bacterial tonsillitis
H0351	Acute staphylococcal tonsillitis

The NHS Clinical Terminology Browser (Browser-5-byte Version 2 Read Codes) was used to identify Read codes for MUPS. The NHS Clinical Terminology Browser was searched using names of included MUPS and other related terms as key words (e.g. headache or tension headache). Table 5.3 presents selected examples of Read codes and terms that were identified using some MUPS such as vomiting, constipation and chest pain as key terms. All Read codes and terms for included MUPS are listed under appendix 4.

Read coded GP consultations referring to Read code chapters 1 and 2 (history/signs and examination or signs) from the process of care codes were included in the analysis. Records with Read codes referring to chapters 0 and 3-9 were excluded from analysis because these codes refer to administrative records, therapeutic and diagnostic procedures that occurred outside of consultations (see appendix 3).

Table 5.3. Examples of Read codes and terms for some MUPS

Key term	Read code	Read term
Vomiting	R0701	[D]Vomiting
	199..	Vomiting symptoms
	1992.	Vomiting
	199Z.	Vomiting NOS
	J16y5	Functional vomiting
	Eu505	[X]Psychogenic vomiting
	E2754	Psychogenic vomiting NOS
	E2642	Cyclical vomiting – psychogenic
Constipation	19C..	Constipation symptom
	19C2.	Constipated
	19CZ.	Constipation NOS
	E2645	Psychogenic constipation
	J520.	Constipation – functional
Chest pain	R065.	[D]Chest pain
	R0650	[D]Chest pain, unspecified
	R065B	[D]Non cardiac chest pain
	R065z	[D]Chest pain NOS
	1828.	Atypical chest pain
	182Z.	Chest pain NOS

Recorded consultations with Read codes under diagnosis chapters A to Z were included in the analysis. Same day GP consultations for patients that have had more than one recorded morbidity code were excluded from analysis. This is because determining the main reason for patient encounter with the GP when more than one morbidity code is recorded in the same day is not straightforward. For example, for a patient with same day GP consultations with morbidity codes referring to elevated blood pressure and headache, it is difficult to establish the

main reason for encounter in that visit. Similarly, this applies to a child with Read codes referring to fatigue symptom and common cold symptoms.

GP consultations were classified and counted as GP consultations for included MUPS if symptoms diagnosis were coded as the main reason for encounter. Vague or unspecific symptoms are usually recorded and coded in GP computer system as symptom diagnoses or non-specific conditions when a precise diagnosis for physical symptoms is unavailable (e.g. unspecific chest pain with normal electrocardiography (ECG) or LBP without urinary symptoms or history of trauma). The free-text records entered for each GP consultation were reviewed to judge whether physical symptoms were MUPS. Physical symptoms with abnormal pathological changes on physical examination or diagnostic testing were not classified as consultations for MUPS. For example, a girl who consulted a GP with abdominal pain, where free-text records stated that the girls also complained of difficulty urinating, had abnormal urine test (presence of protein, leucocytes, and blood) and treated with antibiotics, this consultation was not classified as a consultation for abdominal pain because the free-text information suggest that the girl had a urinary tract infection. Another example of GP consultations that were not classified as a GP consultation for MUPS is when a patient had consulted a GP for diarrhoea after starting antibiotics which was prescribed for respiratory infection.

All consultations for physical symptoms as a result of trauma or injury were not included in the analysis as GP consultations for MUPS. Also, GP consultations for physical symptoms by pregnant women were not counted as consultations for MUPS because it is considered normal for pregnant women to present with transient physical symptoms such as back pain or abdominal pain. Table 5.4

presents more examples of GP consultation that were either classified as MUPS or not.

Table 5.4. Examples of GP consultations that were included or excluded as consultations for MUPS

	Consultation was classified as consultation for MUPS	**Consultation was not classified as consultation for MUPS**
Physical symptom	**Free text record**	**Free text record**
Back pain	No urinary symptoms or trauma	Road traffic accident or trauma
Abdominal pain	No urinary symptoms, trauma, or pregnancy	Positive urine test for urinary tract infection, trauma, pregnancy, or history of untreated ovarian cyst. Abdominal pain associated with hernia endometriosis, food poisoning, peptic ulcer, or eradication therapy
Chest pain	Normal ECG with no other cardiopulmonary symptoms or trauma	Trauma, abnormal ECG, presence of other cardiopulmonary symptoms, or chest pain associated with productive cough
Palpitation	Normal ECG with no history of arrhythmias	Abnormal ECG with history of arrhythmias
Hyperventilation	Not associated with cough, respiratory tract infections or disorders, or history of asthma	Associated with cough, respiratory tract infections or disorders, or history of asthma
Diarrhoea	No history of recent travel, antibiotics use, or indications for food poisoning	Associated with starting antibiotic treatment, on chemotherapy for cancer, history of recent travel, or indications for food poisoning (e.g. all family members had it)
Difficult or painful urination	Not associated with urinary tract infection or other genitourinary tract disorders (e.g. prostate cancer)	Associated with urinary tract infection or abnormal urine test, history of prostate cancer or cystitis, high temperature
Constipation	Not associated with any gastrointestinal disorders or medications use	Associated with gastrointestinal disorders or due to side effects of medications e.g. morphine

5.5.2. Painful and not-painful MUPS

The included list of MUPS will be categorised into painful and not-painful MUPS in some analyses in the next chapters. Painful MUPS are those MUPS that are associated with pain sensation. These include: abdominal pain, headache, back pain, pain in extremities, joint pain, sore muscles including other musculoskeletal pain, painful urination, and painful menstruation. The other MUPS were categorised as not-painful MUPS.

5.6. Indices of Multiple Deprivation

The English Index of Multiple Deprivation 2007 (IMD 2007) will be used within this thesis to as measure for area level deprivation for included children. The term “multiple deprivation” refers to the level deprivation which is measured using separate dimensions or domains experienced by people living in a local area (Department for Communities and Local Government, 2007). The local area can be characterised as deprived as compared to other local areas in a particular domain of deprivation or overall level of deprivation based on the proportion of individuals in that local area experiencing the type of deprivation of interest (Department for Communities and Local Government, 2011).

In the UK, there are no UK-wide indices of multiple deprivation. Each of the four nations in the UK produces its own national indices of multiple deprivation. These include: English Indices of Multiple Deprivation, Northern Ireland Multiple Deprivation Measure, Scottish Index of Multiple Deprivation, and Welsh Index of Multiple Deprivation (Office for National Statistics, 2012a).

The IMD 2007 has been constructed by the Social Disadvantage Research Centre at the University of Oxford and published by Department of Communities and Local Government (Department for Communities and Local Government, 2007). The IMD 2007 contains seven domain indices measured at small geographic areas referred to as Lower Layer Super Output Area (LSOA). These seven domain indices include:

- Income
- Employment
- Health Deprivation and Disability
- Education, Skills and Training
- Barriers to Housing and Services
- Crime
- Living Environment

The overall IMD is conceptualised as a weighted area level aggregation of weights for these seven domains of deprivation (Department for Communities and Local Government, 2007). Table 5.5 shows the domain weights used in the IMD 2007.

In the IMD 2007, for each domain of deprivation and the overall IMD, a score and rank have been assigned to all LSOAs in England (*n*= 32482) (Department for Communities and Local Government, 2007). The IMD scores are usually presented as quintiles with 1 representing the most affluent areas and 5 the most deprived areas (Office for National Statistics, 2012a, Office for National Statistics, 2012b). Within this thesis, the IMD 2007 scores for area level deprivation for

included children will be presented as quintiles, with 1 representing the most affluent and 5 representing the most deprived.

The LSOAs for children's residential areas were extracted from the DiPCA database and were then linked to their IMD 2007 scores. IMD 2007 scores range from 0% to 100% where higher scores indicate greater deprivation.

Table 5.5. Domains and their weights used in the IMD 2007

Domain	Domain Weight
Income Deprivation Domain	22.5%
Employment Deprivation Domain	22.5%
Health Deprivation and Disability Domain	13.5%
Education, Skills and Training Deprivation Domain	13.5%
Barriers to Housing and Services Domain	9.3%
Crime Domain	9.3%
Living Environment Deprivation Domain	9.3%

Source: Department for Communities and Local Government (2007)

5.7. Definition for frequent GP consultation in children

There is no generally accepted definition of frequent GP attendance (Vedsted & Christensen, 2005). Based on existing literature, there are two main methods which have been used to define frequent GP consultation (Vedsted & Christensen, 2005, Gill & Sharpe, 1999). One method is to define a proportional cut-off point (percentage or percentile) in the distribution of consultation frequency and then define patients with consultation frequency higher than that cut-off point as

“frequent consulters” and those with consultation frequency lower than the cut-off point as “non-frequent consulters”. The other method is to arbitrarily choose an absolute number of consultations in a specified time as a cut-off point, and then define frequent and non-frequent consulters based on that cut-off point.

In this thesis, frequent GP consulter children were defined as those whose annual GP consultation rate ranked nearest to the top 10% stratified by child age groups and sex based on the work by Smits and colleagues (2008). All other children whose annual GP consultation frequency ranked below the top 10th centile of their sex and age group were defined as non-frequent GP consulters. The reason for this is that a proportional threshold (top 10%) allows for more meaningful comparison between GP practices, regardless of any variations between practices in consultation rates (Vedsted & Christensen, 2005). Also, research evidence suggests that the best method for identifying frequent consulters is to account for gender and age by dividing patients into at least three age groups per sex (Smits et al., 2008).

5.8. Summary

This chapter has presented operational definitions for a family, a GP consultation, MUPS, and GP consultations for MUPS. Also, the methods used for identifying family members of index children and characteristics of households in the CiPCA database were presented. Additionally, an overview of the English indices of multiple deprivation was give, and frequent GP consultation in children was operationally defined. The next chapter focuses on the second objective of

this thesis by describing the epidemiology of GP consultation for MUPS among children registered with the CiPCA GP practices.

Chapter 6. The epidemiology of MUPS among children in primary care

6.1. Introduction

This chapter presents the results of a study describing the epidemiology of GP consultations for MUPS in 5579 children aged between 0 and 14 years in 2007 and registered with 12 GP practices. The baseline sociodemographic description of children and their mothers is presented. The annual GP consultation prevalence for physic MUPS, the proportion of GP consultations for MUPS in children, and the proportion of children who consulted for MUPS grouped by body system, anatomical site, and type are also presented. Differences in the sociodemographic characteristics between consulters and non-consulters for MUPS are then described. Summary of findings, comparisons with previous studies, interpretation of findings, and strengths and limitations of the study are also presented.

6.2. Aims and objectives

This chapter aims to describe the epidemiology of MUPS among children presenting in primary care. The specific objectives include:

1. To determine the annual GP consultation prevalence for MUPS among children in 2007.
2. To determine the proportion of GP consultations for MUPS as a percentage of all GP consultations in 2007.

3. To determine the proportion of children who consulted for MUPS according to body system and anatomical site, and compare them between sexes and child age groups.
4. To assess whether there are any differences between girls and boys and child age groups in numbers of GP consultations for MUPS, including painful and not painful MUPS, and numbers of different MUPS.
5. To investigate differences between consulters and non-consulters for MUPS in baseline socio-demographic characteristics and GP consultation frequency.

6.3. Methods

6.3.1. Setting

The setting was 12 GP practices contributing to the CiPCA database; see section 5.2.1 for detailed description of the CiPCA database.

6.3.2. Subjects

Children aged 0 to 14 years on 31 December 2007 and registered with any of the 12 GP practices from the CiPCA database were included. The reason for including children aged 0 to 14 years in this chapter is because the research in this thesis is based only on the randomly selected index children from the CiPCA practices (see sections 5.3.1 to 5.3.2). In chapters 7 and 8, children were included when they were aged 2 to 16 years in 2009 in order to examine the association

between GP consultations for MUPS in children and previous exposure parental GP consultations for MUPS in the preceding two years (2007 to 2008). Therefore, to assess their GP consultation patterns for MUPS when they were aged 0 to 1 year and ensure that this thesis covers children across age range, this chapter included children when they were aged 0 to 14 years in 2007.

6.3.3. Data collection

6.3.3.1. Sociodemographic characteristics

The child's date of birth and sex, and mother's date of birth, were extracted from the medical records contained in the CiPCA database. The ages of children and their mothers were determined as on 31 December 2007.

The IMD 2007 scores for each child's residential area were extracted from the Demographics in Primary Care Archive database (DiPCA), which holds demographic data on all patients in the CiPCA database.

The child's birth order and household members' count were determined based on the methods used to identify family members for index children described under section 5.3.1. The birth order of the child was classified as "first" if the child had no siblings or the child was the oldest child in the household (with no other household members' meeting the definition for a sibling (including siblings older than 16 years of age) as defined under section 5.2.1). The birth order of all other children not meeting this definition was coded as "not first".

6.3.3.2. Identification of GP consultations for MUPS

To identify GP consultations for MUPS among children, their recorded GP consultations in the period between 1 January 2007 and 31 December 2007 (both days inclusive) were extracted from the CiPCA database. Relevant GP consultations for MUPS were identified using Read codes relating to the list of included MUPS (see box 5.1). Detailed description of the methods used to identify GP consultations for MUPS are presented under section 5.5.1. Appendix 4 presents the Read codes and terms for included MUPS.

6.3.3.3. The child's GP consultation frequency

All GP consultations made by children for any reason in 2007 were identified and categorised into frequent and non-frequent GP consulters based on the operational definition for frequent GP consultation presented under section 5.7.

6.3.3.4. The annual GP consultation prevalence for MUPS

The annual consultation prevalence for MUPS was defined as the proportion of all children who had consulted a GP at least once for any of the included MUPS in 2007. Children were counted only once if they made more than one GP consultation for MUPS. The denominator included all children who consulted a GP at least once for any reason in 2007.

6.3.3.5. Proportion of GP consultations for MUPS

The proportion of GP consultations for MUPS was calculated as a percentage of all GP consultations made by children in 2007. This represents a measure of relative GP workload related to GP consultations for MUPS in children.

6.3.3.6. MUPS according to body system, specific symptoms, and type

To determine the proportions of children who consulted for MUPS according to body system, specific symptoms, and type (painful and not-painful, see section 5.5.2 for their definitions), the following information was extracted from their recorded GP consultations in 2007:

- Number of all GP consultations for MUPS, including number of consultations for MUPS sorted by body system, specific MUPS, and type. MUPS were grouped under five body systems; musculoskeletal, gastrointestinal, cardiopulmonary, urogenital, and neurological MUPS; see box 5.1 for more details.
- Number of different MUPS; all and according to body system, specific MUPS, and type. Children were counted only once if they made more than one GP consultation for MUPS for those categories (body system, specific MUPS, and type).

6.3.4. Analysis

Children were categorised into three age groups: 0 to 4 years, 5 to 9 years, and 10 to 14 years. The mothers were categorised into four age groups (17 to 27, 28 to 37, 38 to 47, and 48 to 58 years). Fathers were also categorised into four age groups (20 to30, 31 to 41, 42 to 52, and 53 to 63 years). The reason for categorising children and parents into different age groups with roughly similar age bands in each age is to facilitate the analysis and interpretation of the findings.

The IMD 2007 scores for children's residential area level deprivation were presented as quintiles with '1' representing the most affluent and '5' presenting the most deprived area. To categorise children into two groups, according to with their household members' count, with roughly equal proportions in each group, a cut-off of three members per household was used. The child's household members' count was therefore categorised into two groups, with three members or less and with more than three members. As presented in chapter 5, 49.5% of the CiPCA households had three members or less (see figure 5.5).

Numbers of GP consultations for MUPS were categorised into three groups (1, 2, and >2), and numbers of different MUPS were categorised into two groups (1 and > 1). Numbers of GP consultations for painful and not-painful MUPS were grouped as 0, 1, 2, and >2 consultations. Numbers of different MUPS for painful and not painful MUPS were categorised as 0, 1, and >1 MUPS.

Descriptive statistics were used to describe the basic sociodemographic characteristics of children and their mothers. The chi-square test and t-test were used to examine any significant differences between consulters and not-consulters

for MUPS according to their baseline sociodemographic characteristics. Crude ORs with 95% CIs were reported when used to summarise the strength of association between the child's socio-demographic variables and GP consultation status (yes, no) for MUPS.

6.4. Results

6.4.1. Socio-demographic characteristics of children

A total of 5579 children who consulted a GP at least once in 2007 were included in this analysis. Table 6.1 presents the sociodemographic characteristics of children and parents.

The children's mean age was 6.6 years with a standard deviation (SD) of 4.5 years. The proportion of children aged 0-4 years (40.4%) was higher than the proportions of children aged 5-9 years and 10-14 years (27.6% and 32.0%), respectively. The sex distribution of children was split fairly evenly between boys and girls. The maternal mean age was 35 years (SD 7.4) and the paternal mean age was 38 years (SD 7.5). Mothers of 151 children (2.7%) and father of 2367 children (42.4%) were unknown, but all children had at least one parent identified. Both parents of 54.9% of all children (n= 3061) were identified. About 61.1% of mothers aged between 17 and 37 years, and 68.3% of fathers aged between 20 and 41 years. The birth order of 58.4% of children was "first". 48.4% of children were living in households with 4 members or more. IMD 2007 scores for 10 households were unmatched based on the household's postcode.

Table 6.1. Characteristics of children and parents

Variable	Number (%) or mean (SD)
Number of children	5579
Child age (years)	6.6 (4.5)
Child age group (years)	
0-4	2255 (40.4)
5-9	1540 (27.6)
10-14	1784 (32.0)
Female gender	2735 (49)
Mother age (years)	35 (7.4)
Mother age group (years)	
17-27	992 (17.8)
28-37	2318 (41.5)
38-47	1887 (33.8)
48-58	231 (4.1)
No maternal records	151 (2.7)
Father age (years)	38.1 (7.5)
Father age group (years)	
20-30	502 (9.0%)
31-41	1693 (30.3%)
42-52	916 (16.4%)
53-63	101 (1.8%)
No paternal records	2367 (42.4%)
Child birth order	
First	3257 (58.4)
Household member count	
>3	2703 (48.4)
IMD 2007 rank	
Quintile 1 (most affluent)	1167 (20.9)
Quintile 2	1064 (19.1)
Quintile 3	1136 (20.4)
Quintile 4	1075 (19.3)
Quintile 5 (most deprived)	1127 (20.2)
Households with unmatched to IMD 2007 score	10 (0.2)

6.4.2. Annual GP consultation prevalence and proportions of GP consultations for MUPS

A total of 14773 GP consultations were made by children in 2007 for all reasons. Around 21% of all children who had consulted in 2007 had consulted for 1 or more GP consultations for MUPS. About 12% of all GP consultations were consultations for MUPS. 72% of children had only one GP consultation for MUPS, 17% of children had two GP consultations for MUPS, and the remaining children (11%) had 3 or more GP consultations for MUPS.

6.4.3. Proportions of children who consulted for specific MUPS

Table 6.2 presents the proportion of children who consulted at least once for MUPS, presented by body system and anatomical site, among those children who presented with MUPS. Differences in the proportions between sexes and age groups are also presented.

Gastrointestinal, musculoskeletal, and neurologic MUPS were the most common presenting MUPS in all children.

In all children, the three most common MUPS were abdominal pain (24.8%), vomiting (15.2%), and headache (15.2%). Some gender specific differences were observed. The three most common MUPS among girls were abdominal pain (27.3%), constipation (16.2%), and vomiting (14.4%), whereas in boys the three most common MUPS were abdominal pain (22.1%), vomiting (16%), and diarrhoea (12%). The most frequent MUPS varied according to the child age group. Vomiting, constipation, and abdominal pain were the most common MUPS

in children aged 0-4 years, whilst abdominal pain, headache, and joint pain were the most common MUPS among children aged 10-14 years (see table 6.2).

6.4.4. Numbers of GP consultations for MUPS

Table 6.3 shows the numbers of GP consultations for MUPS according to gender and age group. As shown in table 6.3, the numbers of GP consultations for MUPS were comparable between girls and boys. The numbers of different MUPS were also similar between girls and boys. However, there were marked differences between different age groups in numbers of GP consultations for MUPS and numbers of different MUPS. Children aged 10 to 14 years had higher proportions of GP consultations for MUPS and GP consultations for painful MUPS than in other age groups.

Similar differences were also found between different child age groups for number of different MUPS and number of different painful MUPS. Reversed patterns of differences between child age groups and number of GP consultations for not-painful and number of different not-painful MUPS were found, in which younger children consulted more.

Table 6.2 Proportions of all children consulting at least once for specific MUPS by sex and age group

		Gender		Child age group (years)		
	All children (n= 1186)	**Girls (n=611)**	**Boys (n= 575)**	**0 to 4 (n= 423)**	**5 to 9 (n= 271)**	**10 to 14 (n= 492)**
MUPS	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
Gastrointestinal	**695 (58.6)**	**367 (60.1)**	**328 (57.0)**	**357 (84.4)**	**167 (61.6)**	**171 (34.8)**
Abdominal pain	294 (24.8)	167 (27.3)	127 (22.1)	97 (18.7)	93 (34.3)	122 (24.8)
Vomiting	180 (15.2)	88 (14.4)	92 (16.0)	127 (30.0)	26 (9.6)	27 (5.5)
Constipation	161 (13.6)	99 (16.2)	62 (10.8)	98 (23.2)	43 (15.9)	20 (4.1)
Diarrhoea	118 (9.9)	49 (8.0)	69 (12.0)	91 (21.5)	14 (5.2)	13 (2.6)
Nausea	20 (1.7)	10 (1.6)	10 (1.7)	3 (0.7)	7 (2.6)	10 (2.0)
Musculoskeletal	**221 (18.6)**	**102 (16.7)**	**119 (20.7)**	**21 (5.0)**	**42 (15.5)**	**158 (32.1)**
Pain in extremities	73 (6.2)	29 (4.7)	44 (7.7)	13 (3.1)	19 (7.0)	41 (8.3)
Joint pain	73 (6.2)	30 (4.9)	43 (7.5)	7 (1.7)	13 (4.8)	53 (10.8)
Back pain	42 (3.5)	22 (3.6)	20 (3.5)	1 (0.2)	8 (3.0)	33 (6.7)
Chest pain	41 (3.5)	17 (2.8)	24 (4.2)	0 (0.0)	11 (4.1)	30 (6.1)
Other musculoskeletal pain	57 (4.8)	35 (5.7)	22 (3.8)	7 (1.7)	8 (3.0)	42 (8.5)
Neurologic	**156 (13.2)**	**81 (13.3)**	**75 (13.0)**	**11 (2.6)**	**32 (11.8)**	**113 (23.0)**
Headache	118 (15.2)	66 (10.8)	52 (9.0)	3 (0.7)	26 (9.6)	89 (18.1)
Fainting/dizziness	37 (3.1)	20 (3.3)	17 (3.0)	4 (0.9)	6 (2.2)	27 (5.5)
Visual disturbances	8 (0.7)	3 (0.5)	5 (0.9)	1 (0.2)	1 (0.4)	6 (1.2)
Seizure/convulsion	6 (0.5)	2 (0.3)	4 (0.7)	3 (0.7)	1 (0.4)	2 (0.4)
Cardiopulmonary	**37 (3.1)**	**21 (3.4)**	**16 (2.8)**	**9 (2.1)**	**9 (3.3)**	**19 (3.9)**
Hyperventilation	33 (2.8)	17 (2.8)	16 (2.8)	9 (2.1)	8 (3.0)	16 (3.3)
Palpitation	6 (0.5)	5 (0.8)	1 (0.2)	0 (0.0)	1 (0.4)	5 (1.0)

		Gender		Child age group (years)		
	All children (n= 1186)	**Girls (n=611)**	**Boys (n= 575)**	**0 to 4 (n= 423)**	**5 to 9 (n= 271)**	**10 to 14 (n= 492)**
MUPS	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
Urogenital	**31 (2.6)**	**17 (2.8)**	**14 (2.4)**	**10 (2.4)**	**12 (4.4)**	**9 (1.8)**
Painful/difficult urination	38 (3.2)	21 (3.4)	17 (3.0)	13 (3.1)	13 (4.8)	12 (2.4)
Fatigue	**46 (3.9)**	**23 (3.8)**	**23 (4.0)**	**15 (3.5)**	**9 (3.3)**	**22 (4.5)**

Table 6.3. Proportions of all children with each number of GP consultations for MUPS

		Gender		Child age group (years)		
	All children (n= 1186)	**Girls (n=611)**	**Boys (n= 575)**	**0 to 4 (n= 423)**	**5 to 9 (n= 271)**	**11 to 14 (n= 492)**
MUPS	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
All MUPS						
Number of GP consultations						
1	885 (72.1)	437 (71.5)	418 (72.7)	301 (71.2)	213 (78.6)	341 (69.3)
2	201 (16.9)	106 (17.3)	95 (16.5)	67 (15.8)	36 (13.3)	98 (19.9)
>2	130 (11.0)	68 (11.1)	62 (10.8)	55 (13.0)	12 (8.1)	53 (10.8)
Number of MUPS						
1	1044 (88.0)	535 (87.6)	509 (88.5)	387 (91.5)	226 (83.4)	424 (84.1)
=>2	142 (12.0)	76 (12.4)	66 (11.5)	36 (8.5)	45 (16.6)	78 (15.9)
Painful MUPS						
Number of GP consultations						
0	506 (42.7)	256 (41.9)	250 (43.5)	302 (71.4)	95 (35.1)	109 (22.2)
1	512 (43.2)	273 (44.7)	239 (41.6)	98 (23.2)	143 (52.8)	271 (55.1)
2	113 (9.5)	54 (8.8)	59 (10.3)	18 (4.3)	22 (8.1)	73 (14.8)
>2	55 (4.6)	28 (4.6)	27 (4.7)	5 (1.2)	11 (4.1)	39 (7.9)
Number of painful MUPS						
0	506 (42.7)	256 (41.9)	250 (43.5)	302 (71.4)	95 (35.1)	109 (22.2)
1	629 (53.0)	327 (53.5)	302 (52.5)	119 (28.1)	163 (60.1)	347 (70.5)
=>2	51 (4.3)	28 (4.6)	23 (4.0)	2 (0.5)	13 (4.8)	36 (7.3)
Not-painful MUPS						
Number of GP consultations						
0	614 (51.8)	316 (51.7)	298 (51.8)	101 (23.9)	160 (59.0)	353 (71.7)
1	432 (36.4)	217 (35.5)	215 (37.4)	229 (54.1)	91 (33.6)	112 (22.8)
2	89 (7.5)	50 (8.2)	39 (6.8)	51 (12.1)	16 (5.9)	22 (4.5)
>2	51 (4.3)	28 (4.6)	23 (4.0)	42 (9.9)	4 (1.5)	5 (1.0)

		Gender		Child age group (years)		
	All children (n= 1186)	**Girls (n=611)**	**Boys (n= 575)**	**0 to 4 (n= 423)**	**5 to 9 (n= 271)**	**11 to 14 (n= 492)**
MUPS	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
Number of not-painful MUPS						
0	614 (51.8)	316 (51.7)	298 (51.8)	101 (23.9)	160 (59.0)	353 (71.7)
1	532 (44.9)	276 (45.2)	256 (44.5)	294 (69.5)	107 (39.5)	131 (26.6)
=>2	40 (3.4)	19 (3.1)	21 (3.7)	28 (6.6)	4 (1.5)	8 (1.6)

6.4.5. Differences between children in sociodemographic variables

As shown in table 6.4, significant differences in age were found between consulters and non-consulters for MUPS. Children who consulted for MUPS were older (mean= 7.2 years (SD= 4.8) than children who did not consult for MUPS (6.4 (4.4)), *p*= <0.001). Chi-square tests showed that children aged 10 to 14 years had higher odds of consulting for MUPS than children aged 5 to 9 years (crude OR 1.78, 95% CI 1.51 to 2.11) and 0 to 4 years (crude OR 1.65, 95% CI 1.42 to 1.91).

Children who consulted for MUPS were also more likely to have older mothers (*p*= 0.002) and fathers (*p*= 0.033) than children who did not consult for MUPS.

Higher proportions of children who have consulted for MUPS were frequent consulters (19.5%) than children who have not consulted for MUPS (7%), *p*<0.001.

No other significant baseline differences between consulters and non-consulters for MUPS and other variables were found, including sex, child birth order, household members' count, IMD 2007 rank.

Table 6.4. Baseline characteristics of consulters and non-consulters for MUPS

Variable	MUPS consulters (n=1186)	Non-MUPS consulters (n=4393)	p-value
Child age	7.2 (4.8)	6.4 (4.4)	<0.001
Child age group 2007			
0-4 years	423 (35.7%)	1832 (41.7%)	<0.001
5-9 years	271 (22.8%)	1269 (28.9%)	
10-14 years	492 (41.5%)	1292 (29.4%)	
Female	611 (51.5%)	2124 (48.3%)	0.053
Mother age group 2007			
17-27 years	209 (17.6%)	783 (17.8%)	0.002
28-37 years	442 (37.3%)	1876 (42.7%)	
38-47 years	443 (37.4%)	1444 (32.9%)	
48-58 years	60 (5.1%)	171 (3.9%)	
No maternal records	32 (2.7%)	119 (2.7%)	
Father age group 2007			
20-30 years	109 (9.2%)	393 (8.9%)	0.033
31-41 years	342 (28.8%)	1351 (30.8%)	
42-52 years	215 (18.1%)	701 (16.0%)	
53-63 years	31 (2.6%)	70 (1.6%)	
No paternal records	489 (41.2%)	1878 (42.7%)	
Child birth order			
First	692 (58.3%)	2565 (58.4%)	0.980
Not first	494 (41.7%)	1828 (41.6%)	
Household members' count			
≤3	612 (51.6%)	2264 (51.5%)	0.968
>3	574 (48.4%)	2129 (48.5%)	
IMD 2007quartiles			
I (most affluent)	245 (20.0%)	922 (21.0%)	0.745
II	218 (18.7%)	846 (19.3%)	
III	232 (19.9%)	904 (20.6%)	
IV	235 (20.1%)	840 (19.1%)	
V (most deprived)	252 (21.6%)	875 (19.9%)	
Missing IMD score	4 (0.3%)	6 (0.1%)	
Child GP consultation frequency			
Non-frequent consulter	955 (80.5%)	4085 (93.0%)	<0.001
Frequent consulter	231 (19.5%)	308 (7.0%)	

6.5. Discussion

6.5.1. Summary of main findings

This study included 5579 children who consulted a GP at least once for any reason in 2007. The results showed that GP consultations for MUPS are very common among children. The annual consultation prevalence for MUPS in children was 21%. Around 12% of all GP consultations were consultations for MUPS, which represent a considerable workload in primary care.

Gastrointestinal, musculoskeletal, and neurologic MUPS were the most common MUPS groups in children who consulted for MUPS. Abdominal pain, vomiting, and headache were the most common MUPS among children.

No significant differences between girls and boys were found in the number of GP consultations for MUPS.

One finding was that older children had higher numbers of GP consultations for MUPS and number of different MUPS. Similarly, older children had more GP consultations for painful MUPS and number of different MUPS than younger children. However, this trend was reversed in not-painful MUPS, for which younger children consulted more.

Children who consulted for MUPS were more likely to be older and have older parents compared to children who did not consult for MUPS. Children aged 10 to 14 years had 65% and 78% increased odds of consulting for MUPS than children aged 0 to 4 and 5 to 10 years, respectively.

6.5.2. Comparison with other studies

There are few studies on MUPS among children in the primary care setting and in particular there is a lack of studies reporting on annual GP consultation prevalence for MUPS among children. As far as the author is aware, this is the first study to describe the epidemiology of MUPS in primary care using a comprehensive list of MUPS among children aged 0 to 14 years. Previous studies of MUPS among children in primary care have focused only on specific MUPS such as musculoskeletal pain and abdominal pain in specific age groups.

The findings of this study showed that abdominal pain, vomiting and headache were the most common MUPS among children who presented with MUPS in primary care, which is in agreement with previous studies in both primary care (Cardol et al., 2006b) and general populations settings (Rask et al., 2009, Roth-Isigkeit et al., 2005, Perquin et al., 2000a).

In this study, the annual GP consultation prevalence for musculoskeletal pain was 18.6%. In a Spanish primary care study of musculoskeletal pain the annual GP consultation prevalence for non-specific musculoskeletal pain, among 317 children aged 3 to 15 years, was lower at 7.6% (de Inocencio, 2004). In the Netherlands, a primary care study of 65671 children aged 1-12 years reported that the annual GP consultation prevalence for abdominal pain, headache, and minor ailments (fatigue, nausea, pain, dizziness, coughing and sneezing) was 2.7% ,1.5%, and 23.4%, respectively (Cardol et al., 2006b). In the current study, the annual GP consultation prevalence was significantly higher for abdominal pain (21.4%) and headache (8.7%), but the annual consultation prevalence for minor

ailments was comparable to that reported by the Cardol study, excluding coughing and wheezing, (27% in this study vs 23.4% in Cardol study). In the current study, the denominator included only children who consulted a GP at least once for any reason, whereas in the above cited studies the denominator consisted of all registered children. Therefore, this may explain the observed variations in the annual GP consultation prevalence for specific MUPS between the current study and the above cited studies.

This study also found that GP consultation for MUPS in children is associated with a considerable workload in primary care, about 12% of GP consultations in children were consultations for MUPS. A primary care study of 1000 GP consultations in children aged 3 to 14 years showed that 4% (excluding GP consultations for MUPS with known aetiology e.g. trauma) of these GP consultations were for musculoskeletal complaints (de Inocencio, 1998). This is comparable to the finding of the current study in which 2.4% of all GP consultations in children were for musculoskeletal MUPS.

The current study found that older children had significantly higher numbers of GP consultations for MUPS and painful MUPS than younger children. This finding also agrees with the results of previous studies. The prevalence of GP consultations for musculoskeletal pain (Roth-Isigkeit et al., 2005, Levy et al., 2004, de Inocencio, 2004) and gastrointestinal symptoms (Roth-Isigkeit et al., 2005, Levy et al., 2004, de Inocencio, 2004) were also reported to increase with age.

This study found no statistically significant relationship between gender and GP consultation for MUPS, which agrees with the findings of prior studies of children

presenting with MUPS in primary care (Roth-Isigkeit et al., 2005, Levy et al., 2004, de Inocencio, 2004).

The current study found no significant baseline differences between consulters and non-consulters for MUPS and area level deprivation. These findings are also consistent with the results of previous studies in primary care and the community. One study from the Netherlands found no association between socioeconomic status and self-reports of use of health care services for chronic benign pain (recurrent/persistent pain for three months or more) among children aged 0 to 18 years (Little et al., 2001, Boey & Goh, 2001c, Perquin et al., 2001, Boey & Goh, 2001a, Campo et al., 2004). Another study from the USA also found no significant relationship between socioeconomic status and child GP attendance for abdominal pain (Little et al., 2001, Boey & Goh, 2001c, Perquin et al., 2001, Boey & Goh, 2001a, Campo et al., 2004). In the UK, a cross-sectional survey in primary care reported a significant association between council house tenancy (a proxy for socioeconomic status) and child GP consultation for MUPS (Little et al., 2001). However, this study compared high GP consulters and non-high GP consulters. Nonetheless, two population-based studies of children in the UK found no relationship between the reporting of widespread pain or back pain and area level deprivation (Jones et al., 2003a, Jones et al., 2003b).

The current study also demonstrated no significant baseline differences between consulters and non-consulters for MUPS and child birth order or household members' count. This finding is consistent with the results of other studies which found no significant relationship between child attendance in primary

care for chronic benign pain or abdominal pain and family size or birth order of the child (Perquin et al., 2001, Huang et al., 2000).

Parents of children who consulted for MUPS were older than parents of children who did not consult for MUPS. However, this is not surprising because older children had more consultations for MUPS than younger children, and we would expect correlation in age between parents and children.

6.5.3. Interpretation

This study shows that MUPS are very common among children presenting in primary care with 1 out of 10 GP consultations in children being related to MUPS. These findings indicate the need for more research to identify the risk factors for MUPS among children presenting in primary care.

Another important finding was that GP consultations for MUPS and the number of different MUPS children consult with (including painful MUPS) increases as the children become older. The exact mechanisms for this association are not fully clear as yet. However, there is some evidence that biological and psychosocial changes during childhood may trigger MUPS in children. As discussed in chapter 2 (section 2.2.3.1), previous studies reported an association between pubertal development and increased reporting of MUPS among children (Aro & Taipale, 1987, Rhee, 2005). Also, an increase in social demands or expectations during childhood, and stress related to schooling, was found to be associated with reporting of MUPS in children (Berntsson & Gustafsson, 2000, Eminson et al., 1996, Perquin et al., 2000b). Additionally, two studies found a link between

increased reporting of headache or abdominal pain and school entry (Alfven, 2003, Anttila et al., 1999).

In the current study, the proportion of children aged 0-4 years who consulted for any reason at least once was higher than the proportions of children in the other two age groups. The likely explanation for this finding is that younger children usually have higher GP consultation rates than older children (Hippisley-Cox & Vinogradova, September 2009). Therefore, younger children were more likely to be identified than older children.

6.5.4. Strengths and limitations of the study

This study included a large number of children aged 0 to 14 years from 12 GP practices, used a comprehensive list of MUPS, and relied on primary care medical records, which are likely to be robust. Additionally, this study used the CiPCA database, which is a high quality dataset (see section 5.2.1) and similar GP consultation rates compared to national GP databases (Porcheret et al., 2004, Jordan et al., 2007).

There are a number of limitations for this study that should be noted here. One limitation is that these GP practices were from North Staffordshire, which is more deprived than the average for England (Jordan et al., 2010). Hence, the results may not be generalisable to children from other more affluent or deprived areas. Also, these findings represent children who had consulted a GP at least once for any reason during 2007. However, most children consult at least once a year (Hippisley-Cox & Vinogradova, September 2009). Additionally, children who

consulted for MUPS were identified using a list of codes for MUPS, so children who consulted for MUPS that were not coded as their chief complaint or they had more than one reason for consultation also remain unidentified. Moreover, there is a potential for diagnostic misclassification of presenting complaints among children consulting in primary care (more detailed discussion of this potential limitation is presented in the next chapter, see section 7.5.4).

6.5.5. Conclusion

This study has shown that GP consultations for MUPS are very common in children, represent a considerable workload in primary care, and increase as children become older. More analytical research is needed to identify the risk factors for GP consultations for MUPS among children. Better understanding of the mechanisms underlying the occurrence and health seeking behaviour for MUPS among children is needed. Such insights may direct the development of better management strategies of children presenting with MUPS in primary care and shed light on interventions that may prevent the development or recurrence of MUPS in children.

Chapter 7. The association between GP consultations for MUPS in parents and children: a case-control study

7.1. Introduction

This chapter investigates whether children previously exposed to parental GP consultations for MUPS are at increased odds of GP consultations for MUPS as compared to unexposed children, and whether this association is different for mothers and fathers. Dose-response relationships between exposure to parental GP consultations for MUPS (the dose) and child GP consultation for MUPS (the response) are also investigated using different levels of dose intensity measures related to parental GP consultations for MUPS. Children who had consulted a GP in 2009, and who had at least one parent who had consulted for any reason between 2007 and 2008 were included.

7.2. Aims and objectives

The primary aim of this chapter is to determine whether GP consultations for MUPS in children are associated with previous exposure to GP consultations for MUPS in their parents. The specific objectives include investigating the following hypotheses:

(1) Children previously exposed to parental GP consultations for MUPS are at increased odds of GP consultations for MUPS than unexposed children.

(2) There will be dose-response relationships between child GP consultations for MUPS and parental: number of GP consultations for MUPS, number of MUPS, number of MUPS reported in each consultation for MUPS, and frequency of parental consultations for MUPS.

(3) Exposure to maternal GP consultation for MUPS has greater influence on the child GP consultation for MUPS than exposure to paternal GP consultation for MUPS.

7.3. Methods

7.3.1. Study design and setting

The design for this study is a case-control approach. This study was conducted in 12 GP practices in North Staffordshire. The total population registered with these practices at mid-year 2009 was 104,911. The overall age-sex structure for CiPCA practices registered populations is similar to age-sex structure of the population in England and Wales reported in the 2011 census data (ONS, 2012). These GP practices contribute to the CiPCA database (see section 5.2.1. for detailed description of the CiPCA database).

7.3.2. Study population

The eligible population for the study included parents and their children registered with the 12 GP practices.

7.3.3. Study period

Figure 7.1 shows the study period over which the association of GP consultation for MUPS between parents and children was investigated. All recorded GP consultations for children in 2009 were used to identify children who had consulted a GP at least once and were eligible to be included in the study. Parental GP consultations for MUPS were defined between 2007 and 2008. The rationale behind using parental consultation data between 2007 and 2008 is to satisfy one of the main concepts of causation in epidemiology which is the temporal sequence of association, which requires the exposure to precede the outcome (Rothman & Greenland, 2005). Also, having two years is more reliable than one, and provides more data to examine the effect of exposure to parental GP consultations for MUPS on the child consultation patterns for MUPS. Additionally, using parental consultation data for at least two consecutive years might be useful for investigating dose-response relationships between parental consultation frequency for MUPS and subsequent child consultation status and number of consultations for MUPS.

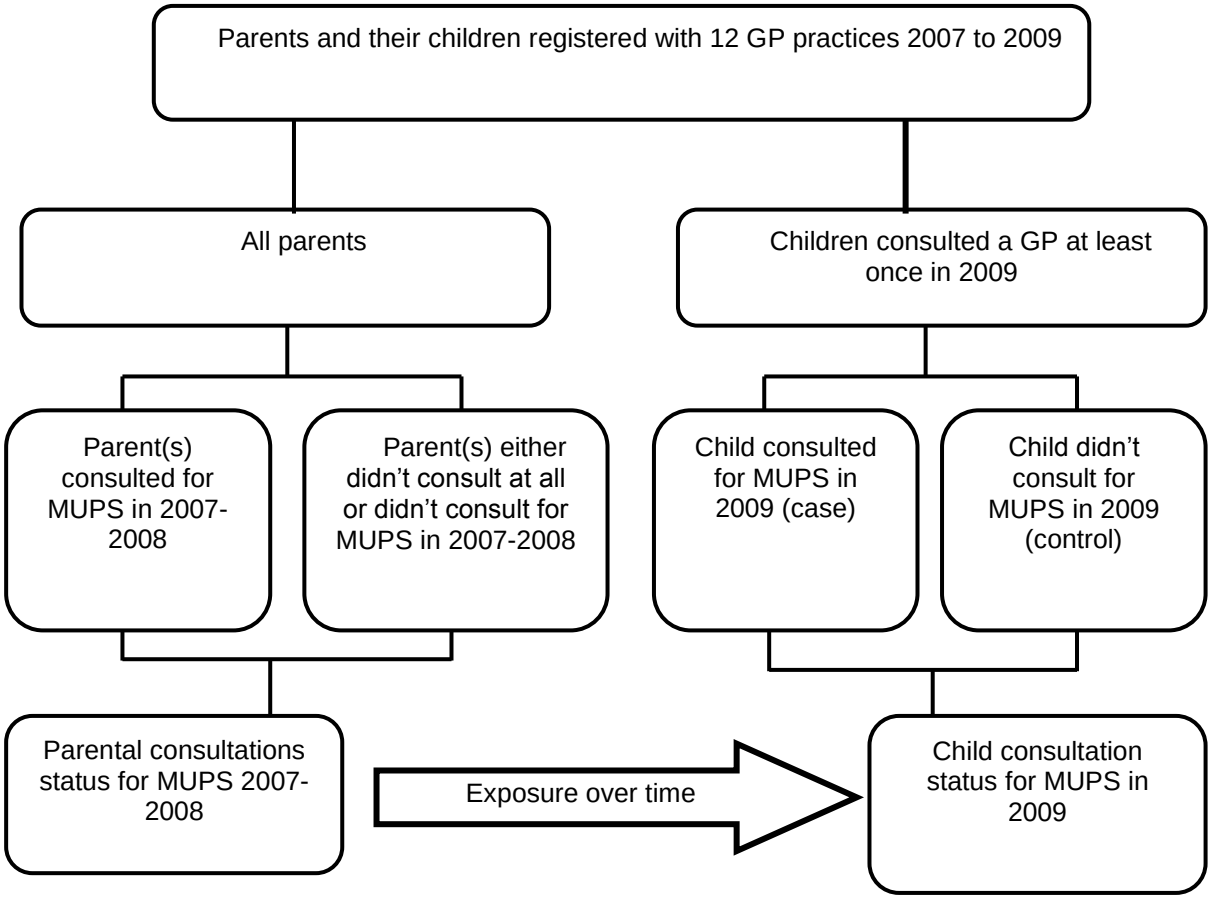
7.3.4. Case-control definition and selection

Potential case and control children were identified using their recorded GP consultations as follows:

- Cases and controls were defined as children aged 2 to16 years on 1st January 2009.

- Cases had at least one recorded GP consultation for MUPS between 31 December 2008 and 31 December 2009.
- Either parent or both were registered with any of the 12 GP practices in the period between 31 December 2006 and 31 December 2008.

Figure 7.1. Study period over which the association of GP consultation for MUPS between parents and children was investigated



7.3.4.1. Case definition and selection

- The child had at least one recorded GP consultation for any of the included MUPS between 31 December 2008 and 31 December 2009. The list of included MUPS for children is presented in box 5.1. Inclusion criteria for MUPS and process of identification of GP consultations for MUPS are also presented under sections 5.5 to 5.5.1.

7.3.4.2. Control definition and selection

- The child had at least one recorded GP consultation between 31 December 2008 and 31 December 2009, but not for MUPS.

7.3.5. Sample size calculation and matching

The sample size was calculated for 80% study power and 95% confidence using EpiCalc 2000 (Gilman, J. & Myatt, M., 1998). Sample size calculations showed that 535 children were required (107 cases and 428 controls) for the study to be able to detect an association for GP consultation for MUPS between parents and children with an odds ratio of 2, assuming the proportion exposed in the control group is 20%, and with 1:4 ratio of cases to controls.

As discussed in section 3.5.3, matching is a common approach used to deal with confounding in case-control studies by increasing the degree of similarity of cases and controls. In this case-control study, matching variables were selected on the basis of literature reports of potential confounding variables as well as the

availability of sufficient number of controls to be matched to cases on those potential confounding variables (Little et al., 2001, Ward et al., 2006, Roth-Isigkeit et al., 2005, Chitkara et al., 2007, Roth-Isigkeit et al., 2004, Perquin et al., 2000b, Levy et al., 2004, Cardol et al., 2006b, de Inocencio, 2004, de Inocencio, 1998, Watson & Kemper, 1995, Tessler, 1980). Therefore, control children were matched to case children on sex, GP practice and maternal age group. Parents and children were categorised intro roughly equal age groups based on their ages on 1 January 2009. Mothers were categorised into four age groups based on their age in 2009 (19 to 29 years, 30 to 40 years, 41 to 51 years, and 52 to 62 years). Similarly, fathers were categorised into four age groups (22 to 32 years, 33 to 43 years, 44 to 54 years, and 55 to 65 years). Children were categorised into three age groups (2 to 6 years, 7 to 11 years, and 12 to 16 years). The child age group was not matched on and will be adjusted for in the analysis where necessary. The reason for this is to explore any interaction effects between the child age group and parental GP consultation for MUPS on the child GP consultation for MUPS. The interaction effect is defined as the effect of two more independent variables in combination on a dependent variable (Field, 2005).

It has been suggested that taking multiple controls per case (up to 3 to 4 controls per case) provides more accurate estimation of exposure frequency to risk factors under study among controls and increases the precision of the ORs, and thus enhances study power to detect associations of interest which truly exist (Taylor, 1986, Kestenbaum, 2009c). So, depending on the availability of suitable controls, one to four controls per case were matched to cases. If more than four controls per case were available per matching strata, four controls per case were

selected at random. The procedure was performed using SPSS for Windows 20.0 (IBM Corp, 2011).

A total of 5308 children, 1328 cases and 3980 controls, were included in the study. Table 7.1 shows the case: control ratio for children included in the study.

Table 7.1. Number of included cases and controls according to each case: control ratio

Case: control ratio	Number of cases	Number of controls
1:1	40	40
1:2	356	712
1:3	500	1500
1:4	432	1728
	Total: 1328	Total: 3980

7.3.6. Data collection for cases, controls, and their parents

Recorded GP consultations in the CiPCA database and demographic data in the DiPCA database were used to extract data on the following variables for children and their parents.

7.3.6.1. Exposure to parental consultations for MUPS

The main exposure of interest was parental GP consultation for MUPS. Parental GP consultation status for MUPS (yes, no) was grouped into four categories in order to examine the hypothesis 7.2.3 (both parents had consulted with MUPS,

only father had consulted with MUPS, only mother had consulted with MUPS, and neither parent consulted with MUPS).

To examine the hypothesis 7.2.2, two components of exposure to parental GP consultations for MUPS were used: dose intensity and dose duration. Three measures of dose intensity and one measure of dose duration were used:

- Number of GP consultations for MUPS in mothers and fathers in 2007 and 2008.
- Number of different presenting MUPS in mothers and fathers in 2007 and 2008.
- Number of presenting MUPS per each GP consultation for MUPS in mothers and fathers in 2007 and 2008.
- Parental consultation frequency for MUPS in 2007 and 2008. Mothers and fathers were categorised into three consultation frequency groups according to their frequency of GP consultations for MUPS between 2007 and 2008:
    - Non-consulters for MUPS: this included mothers or fathers who did not consulted for MUPS between 2007 and 2008.
    - Non-persistent consulters for MUPS: this group included mothers or fathers who had at least one GP consultation for MUPS only in one year, either 2007 or 2008.
    - Persistent consulters for MUPS: this included mothers or fathers who had at least one GP consultation for MUPS in each year (2007 and 2008).

7.3.6.2. Demographic variables

Child sex, and date of birth for both children and their parents were extracted, and their ages on 31 December 2009 were calculated.

7.3.6.3. Potential effect modifiers

Effect modification is defined as a change in the magnitude of an association between the exposure and the disease under investigation which differs according to another factor, which known as effect modifier (Kestenbaum, 2009c). Kestenbaum (2009) discusses that effect modifiers can function as in any study as effect modifiers, confounders, or both. Therefore, it is important to assess for potential effect modifiers in multivariable analyses in order to control for confounding as well as measure and report any effect modification, also known as interaction, (Kleinbaum et al., 2007b).

- Child's birth order and household members' count were determined based on the methods used to identify household members' in the CiPCA database (see section 5.2.2). Household members' count was dichotomised into two categories (households with three members or less and households with more than three members). Birth order of the child was also dichotomised into two categories (first and not-first categories).
- IMD 2007 scores: The IMD 2007 scores for all children ranged from 3.0% to 70.6% and were grouped into quintiles: ≤13.0 (20%), >13.0 to 21.6 (40%), >21.6 to 31.5 (60%), >31.5 to 44.0 (80%), and > 44.0 to 70.6 (100%).

- Parental history of anxiety or depressive disorders: GP consultation records for parents in 2007 and 2008 were searched using Read codes referring to anxiety or depressive disorders to identify parents who were diagnosed with anxiety or depressive disorders. Parental history of anxiety or depressive disorders status (yes, no) was grouped into four categories (both parents had anxiety or depressive disorders, only father had anxiety or depressive disorders, only mother had anxiety or depressive disorders, and both parents had no anxiety or depressive disorders). Parental GP electronic records were searched using a list of Read codes to identify parents with a history of anxiety or depressive (see appendix 5).
- Child's GP consultation frequency in 2009: the child's GP consultation frequency was categorised into two groups, frequent consulters and non-frequent consulters using the method presented under section 5.7.

7.3.7. Statistical analysis

Descriptive statistics were used to describe the sociodemographic and health related characteristics of children and their parents. Also, Chi-squared tests were performed to test for significant baseline differences between cases and controls for categorical variables, and Mann-Whitney U tests were performed for continuous variables. Controls were matched to cases on sex, practice, and maternal age group (see section 7.3.5). Univariable analyses for the association between all variables, excluding matching variables, and the child GP consultations for MUPS were performed using the conditional logistic regression using the COXREG procedure in SPSS, which allows for inclusion of variable

number of controls per case and modelling of time-to-event data. A time-constant variable was created in the data and entered in the “time function” box in the COXREG regression procedure to indicate which children have consulted for MUPS. In this variable, all cases were given a value of 1 indicating that they have consulted for MUPS, and a value of 2 was given to controls to indicate that they were censored at a later time. Multivariable models were then fitted to examine the association between GP consultation for MUPS between parents and children, investigate dose-response relationships, test for any interaction effects between parental GP consultations for MUPS and other included variables on child GP consultation for MUPS, and adjust for potential effect modifiers and other variables that were significantly associated with child GP consultation for MUPS in the univariable analyses. Poisson regression models were also performed to examine dose-response relationships between parental number of GP consultations for MUPS and the child number of GP consultations for MUPS. These analyses included number of GP consultations for MUPS, number of MUPS, and number of MUPS reported in each GP consultation. The multivariable analysis included all variables that were significant with a *p*-value of ≤0.25 in the univariable analyses. The reason for this is that the traditional 0.05 cut-off point used to judge the statistical significance may not identify those variables that are not significantly associated with the dependent variable in univariable analysis, but they become significant predictors of the outcome variable when they are taken in a multivariable analysis collectively (Mickey & Greenland, 1989, Bendel & Afifi, 1977). Therefore, some authors recommend the use of a *p*-value of 0.25 or higher to select independent variables as candidates for a multivariable analysis (Mickey & Greenland, 1989, Hosmer & Lemshow, 2000).

To check for any effects of multicollinearity on adjusted ORs, correlation analyses were performed to examine the strength and direction of the linear relationship between independent variables. The term multicollinearity is defined as the existence of moderate or high correlation between two or more independent variables in a multiple regression model (Simon, 2004). The problem of multicollinearity arises from violation of the general assumption in multiple regression that there should be no perfect or high multicollinearity between any of the predictor variables (Bowers, 2008). Marques de Sá (2007) argues that highly correlated predictors explain much of the same amount of variance in the outcome variable, so it is not possible to separate the effects of the predictor variables on the outcome variable. Subsequently, high degree of multicollinearity leads to imprecise estimates of the values of the affected regression coefficients or ORs, and also the coefficients tend to have large standard errors. A bivariate correlation coefficient (r) of 0.7 or more suggests a high correlation between two independent variables (Pallant, 2011).

7.4. Results

7.4.1. Participants

5308 children were included (1328 cases and 3980 controls). Mothers of 4135 children (77.9%) had consulted a GP at least once between 2007 and 2008. Fathers of 2003 children (37.7%) had consulted a GP at least once in the same period. The fathers of 2250 children (42.4%) were unknown, but all mothers were known.

7.4.2. Sociodemographic and health related characteristics of children and parents

Baseline sociodemographic and health related characteristics of children and their parents are summarised in table 7.2.

Baseline differences between cases and controls were statistically significant for all variables except for IMD quintiles, and father history of anxiety or depressive disorders between 2007 and 2008 (see table 7.2). Case children were slightly older than control children, with a mean age of 9.6 years and 8.3 years, respectively.

The proportion of cases (57.5%) whose birth order was first was slightly higher than that for controls (52.3%). The proportion of cases from household of more than three members was lower (48%) compared to controls (52.1%). Higher proportions of case children were frequent consulters (15.7%) than control children (5.3%).

Cases had a higher proportion (25.2%) of maternal history of anxiety or depressive disorders between 2007 and 2008 than controls (19.9%) and a non-significantly higher proportion (4.9%) of paternal history of anxiety or depressive disorders as compared to controls (4.3%).

Table 7.2. Baseline sociodemographic and health related characteristics of children and their parents

	Cases (n=1328)	Controls (n=3980)	*p*-value
Child age[a]	9.6 (4.7)	8.3 (4.5)	<0.001
Female[b]	739 (55.6%)	2073 (52.1%)	---
Child age group			
2-6 years	428 (32.2%)	1688 (42.4%)	<0.001
7-11 years	325 (24.5%)	1114 (28.0%)	
12-16 years	575 (43.3%)	1178 (29.6%)	
Child birth order			
First	763 (57.5%)	2083 (52.3%)	0.001
Not first	565 (42.5%)	1897 (47.7%)	
Household members' count			
≤3	691 (52.0%)	1908 (47.9%)	0.010
>3	637 (48.0%)	2072 (52.1%)	
IMD 2007quartiles			
I	272 (20.5%)	819 (20.6%)	0.969
II	262 (19.7%)	785 (19.7%)	
III	263 (19.8%)	792 (19.9%)	
IV	280 (21.1%)	809 (20.3%)	
V	244 (18.4%)	759 (19.1%)	
Missing IMD score	7 (0.5%)	16 (0.4%)	
Mother age	38.5 (7.4)	37.4 (7.0)	<0.001
Mother age group[b]			
19-29 years	216 (16.3%)	722 (18.1%)	---
30-40 years	604 (45.5%)	1972 (49.5%)	
41-51 years	475 (35.8%)	1227 (30.8%)	
52-62 years	33 (2.5%)	59 (1.5%)	
Father age	41.1 (7.8)	39.8 (7.6)	<0.001
Father age group			
22-32 years	101 (7.3%)	378 (9.5%)	<0.001
33-43 years	381 (28.7%)	1241 (31.2%)	
44-54 years	246 (18.5%)	590 (14.8%)	
55-65 years	36 (2.7%)	73 (1.8%)	
No paternal records	564 (42.5%)	1698 (42.7%)	
Child GP consultation frequency			
Frequent consulter	208 (15.7%)	210 (5.3%)	<0.001
Non-frequent consulter	1120 (84.3%)	3770 (94.7%)	
Mother history of anxiety or depressive disorder 2007-2008			
Yes	335 (25.2%)	792 (19.9%)	<0.001
No	993 (74.8%)	3188 (80.1%)	
Father history of anxiety or depressive disorder			
Yes	65 (4.9%)	172 (4.3%)	0.386
No	699 (52.6%)	2110 (53.0%)	
No paternal records	564 (42.5%)	1698 (42.7%)[c]	

[a] Data are means (SD) or numbers (%); [b]Significance test of baseline differences between cases and controls for gender and maternal age group was not performed because controls were matched to cases on these variables, with variable number of controls per case; [c]Percentages may not total 100 due to rounding.

7.4.3. The association of GP consultations for MUPS between parents and children

The first analysis included children whether or not both parents were included in the study sample. No association was found between father's GP consultations for MUPS and child consultation for MUPS in both univariable and multivariable analyses; crude OR 0.89, 95% CI 0.73 to 1.09 and adjusted OR 0.85, 95% CI 0.69 to 1.05. These analyses only included children (766 cases and 2292 controls) whose fathers were registered with CiPCA practices.

Another analysis investigated the association between GP consultations for MUPS in mothers and children. The outcome from this analysis showed that cases were more likely than controls to have a mother who had consulted for MUPS (crude OR 1.55, 95% CI 1.37 to 1.76); adjusted OR 1.42, 95% CI 1.24 to 1.63).

In multivariable analyses, the ORs were adjusted for those variables that were significantly associated with child consultation for MUPS in univariable analyses, which include: child age group, child birth order, household members' count, child consultation frequency, and mother's history of anxiety or depressive disorders.

No significant interaction effects between independent variables on the child GP consultation status for MUPS. The interaction effect for child age group and maternal GP consultation for MUPS on the child GP consultation status for MUPS was not statistically significant. This suggests that the effect of maternal GP consultation for MUPS on the child GP consultation for MUPS was the same across the three child age groups.

No independent variables included in the multivariable analyses were highly intercorrelated, which suggest that multicollinearity is not a significant issue for this set of variables. The highest correlation (r= 0.46, n= 5308, *p* <0.000) was found between household members' count and child birth order (not first). This is not surprising because the chance of selecting a child at random from each household whose birth order is not first increases with increasing household members' count.

The second analysis was restricted to those children who had both parents included in the study sample (764 cases and 2183 controls). This analysis showed no significant association between GP consultations for MUPS in fathers and children if only fathers had consulted for MUPS (see table 7.3). There was a significant association between GP consultation for MUPS between mothers and children when only mother had consulted for MUPS, adjusted OR 1.41, 95% CI 1.15 to 1.73. Also, this analysis revealed a significant association between GP consultations for MUPS in both parents and children, adjusted OR 1.52, 95% CI 1.19 to 1.93 (see Table 7.3).

Table 7.3. Parental consultation status for MUPS by cases and controls

	Cases[a] **n (%)**	**Controls** **n (%)**	**Crude OR** **(95% CI)**	**Adjusted OR[b]** **(95% CI)**
Both parents did not consult for MUPS[c,d]	276 (36.1)	989 (45.3)		
Only father consulted for MUPS	78 (10.2)	335 (15.3)	0.82 (0.63 to 1.08)	0.83 (0.63 to 1.11)
Only mother consulted for MUPS	260 (34.0)	568 (26.0)	1.44 (1.20 to 1.74)	1.41 (1.15 to 1.73)
Both parents consulted for MUPS	150 (19.6)[e]	291 (13.3)	1.63 (1.29 to 2.06)	1.48 (1.15 to 1.91)

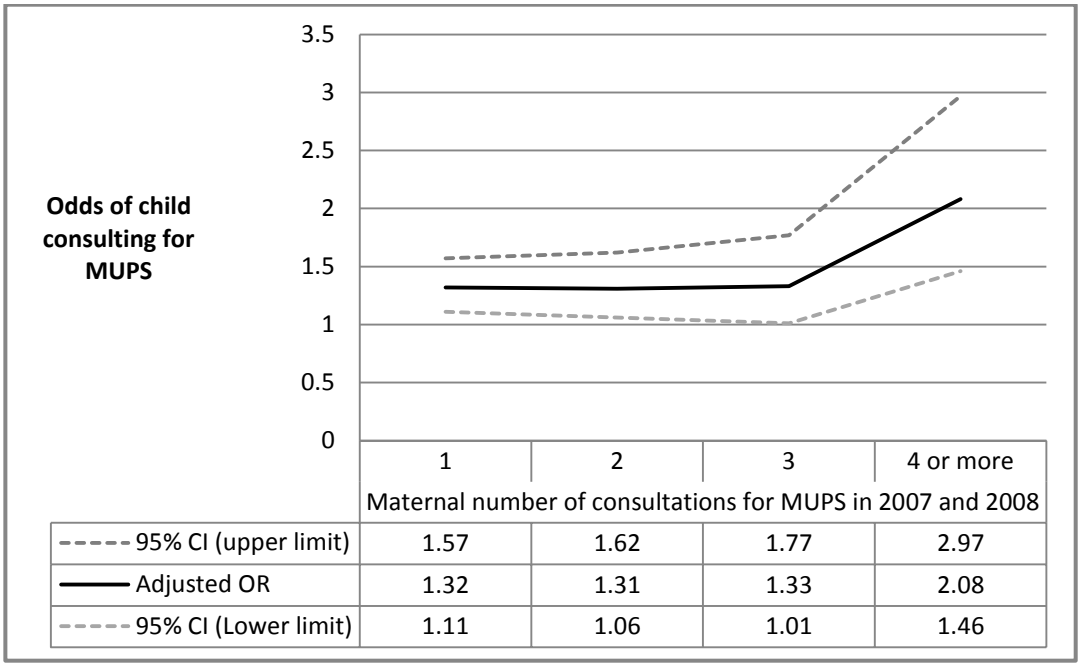
[a]Matched conditional logistic regression analysis; [b]adjusted OR for child age group, household members' count, child consultation frequency, parental psychiatric history; and father age group; [c]Reference category; dMedically unexplained physical symptoms; [e]percentages may not total 100 due to rounding. Case (n= 764) and controls (n=2183).

7.4.4. Dose –response associations between GP consultations for MUPS in parents and children

Analyses for dose-response associations for GP consultations for MUPS between parents and children were restricted to mothers and children because there were no significant associations between GP consultations for MUPS between fathers and children as mentioned above under section 7.4.3. Analyses showed significant dose-response relationships for GP consultations for MUPS between mothers and children for all dose intensity measures and duration. The outcome variable was the child GP consultation status (yes, no) for MUPS. Figure 7.2 shows the relationship between number of GP consultations for MUPS in mothers and child GP consultation status for MUPS; the strongest associations were when the mother had 4 or more GP consultations for MUPS.

Similar patterns of dose-response relationships also emerged for the relationship between maternal consultation frequency for MUPS and child GP consultation status for MUPS (see table 7.4). As shown in table 7.4, cases had higher odds of exposure to maternal persistent consultations for MUPS (adjusted OR 1.67, 95% CI 1.36 to 2.06) and non-persistent consultations for MUPS (adjusted OR 1.34, 95% CI 1.16 to 1.54) than controls.

Figure 7.2. Dose-response relationship between maternal number of GP consultations for MUPS and child consultation status for MUPS



Matched analysis (conditional logistic regression); adjusted for child age group, child birth order, household members' count, child consultation frequency, and maternal psychiatric history. Cases (n=1328) and controls (n=3980)

Table 7.4. Associations between maternal consultation frequency for MUPS and child consultation for MUPS

Maternal consultation frequency group for MUPS	Cases (n=1328)	Controls (n= 3980)	Crude OR[b] (95% CI)[c]	Adjusted[e] OR (95% CI)
NC for MUPS[f,g]	633 (47.7%)[j]	2338 (58.7%)		
NPC for MUPS	481 (36.2%)	1246 (31.3%)	1.42 (1.24, 1.63)	1.34 (1.16, 1.54)
PC for MUPS[i]	214 (16.1%)	396 (9.9%)	1.96 (1.62, 2.38)	1.67 (1.36, 2.06)

[a]Matched conditional logistic regression analysis; [b]Odds ratio; [c]Confidence intervals; [e]Odds ratios were adjusted for child age group, household members' count, child consultation frequency, and mother psychiatric history; [f]Reference category; [g]Non-consulters for MUPS; [h]Non-peristent consulters for MUPS; [i]Persistent consulters for MUPS; [j]Percentages may not total 100 due to rounding.

Poisson regression analyses also showed statistically significant associations between mothers and children for number of consultations for MUPS, number of MUPS, and number of different MUPS reported in each consultation. An increase in maternal GP consultation for MUPS by 1 consultation was associated with 6% higher rate of GP consultation for MUPS in children (adjusted OR 1.06, 95% CI 1.04 to 1.08). Also, an increase in number of different MUPS in the mother by 1 physical symptom was associated with 11% higher rate of GP consultation for different MUPS in children (adjusted OR 1.11, 95% CI 1.07 to 1.15). Furthermore, increase in number of different MUPS reported in each GP consultation for MUPS in the mother was associated with 13% higher rate of reporting different MUPS per each GP consultation for MUPS in children (OR 1.13, 95% CI 1.09 to 1.17).

7.4.5. Sensitivity analysis

A possible limitation for the measure of frequent consultations for MUPS in mothers is that mothers who have consulted for MUPS within a short period of time, such as end of December 2007 and early January 2008, were defined as frequent consulters for MUPS. This may have overestimated the ORs for the relationship between child GP consultation status for MUPS and exposure to frequent maternal GP consultations for MUPS. To check the validity of this measure, all mothers who consulted for MUPS between December 2007 and the end of January 2008 (n= 403) were identified and excluded. Then univariable and multivariable analyses were performed to examine the association between child GP consultations status for MUPS and previous exposure to maternal consultation frequency for MUPS. The crude and adjusted ORs obtained from these analyses

were very similar to those ORs obtained when all mothers were included in the analysis (see table 7.5). This confirms that the measure of frequent consultations for MUPS in mothers was not associated with overestimation of the ORs presented in table 7.4.

Table 7.5. Associations between maternal consultation frequency for MUPS and child consultation for MUPS

Maternal consultation frequency group for MUPS[a]	**Cases (n= 1197)**	**Controls (n= 3708)**	**Crude OR**[b] **(95% CI)**[c]	**Adjusted**[e] **OR (95% CI)**
NC for MUPS[f,g]	633 (52.9%)[j]	2338 (63.1%)		
NPC for MUPS	422 (35.3%)	1111 (30%)	1.39 (1.20, 1.61)	1.30 (1.11, 1.51)
PC for MUPS[i]	142 (11.9%)	259 (7%)	2.04 (1.61, 2.57)	1.71 (1.33, 2.19)

These analyses were performed after excluding data for mothers and children who have consulted between 1 December 2007 and 31 January 2008

[a]Matched conditional logistic regression analysis; [b]Odds ratio; [c]Confidence intervals; [e]Odds ratios were adjusted for child age group, household members' count, child consultation frequency, child birth order, and mother psychiatric history; [f]Reference category; [g]Non-consulters for MUPS [h]Non-peristent consulters for MUPS; [i]Persistent consulters for MUPS; [j]Percentages may not total 100 due to rounding.

7.5. Discussion

7.5.1. Summary of main findings

Analyses in this chapter aimed to investigate the association between parental GP consultations for MUPS and child GP consultations for MUPS. The results of this study showed an increase in the odds of GP consultation for MUPS in children

whose mothers had previously consulted for MUPS. An interesting finding was that no association was found between GP consultations for MUPS in children and exposure to GP consultation for MUPS in their fathers. However, children exposed to GP consultations for MUPS in both parents had higher odds of consultation for MUPS as compared to not-exposed children. This study also showed an increase in the odds of child GP consultation for MUPS with increasing levels of dose intensity of exposure to number of GP consultations for MUPS, number of different MUPS, numbers of different MUPS recorded per consultation, and duration of exposure to GP consultations for MUPS in the mother.

7.5.2. Comparison with existing literature

As mentioned in the systematic review chapter (see section 4.4.1 and table 4.2), there have been only a few published studies that specifically investigated the association of primary care consultation for MUPS between parents and children. As far as the author is aware this the first study to: investigate the association between prior exposure to parental GP consultations for MUPS and child GP consultations for MUPS using primary care consultations data, use a comprehensive list of MUPS, include children aged 2 to 16 years, and investigate dose-response relationships using different measures for dose intensity and duration of exposure.

The finding of this study with respect to the significant association of GP consultations for MUPS between mothers and children is consistent with the findings of the systematic review (4.4.4) which found some evidence of an association between GP consultations for MUPS in parents and children.

As hypothesised, this study found that exposure to GP consultations for MUPS in mothers has a greater influence on the child's GP consultation for MUPS than that in fathers. This important finding broadly agrees with the findings of the very few studies that specifically examined whether the parental influence on the child GP consultation for MUPS is different for mothers and fathers. Cardol and colleagues (2006) found that the association of primary care consultations for abdominal pain or headache was greater for mother-child pairs than father-child pairs. However, in that study, the strength of associations was reported as percentages of shared variance in consultation frequency between parents and children, and therefore, it is not clear whether these associations are statistically significant or not. Another study by Levy and colleagues (2000) investigated whether the child's consultation for GI symptoms was greater if their mother had IBS than if their father had IBS, no significant parental gender differences were found. However, when they examined all parental GP consultations for both GI and non-GI MUPS consultations, mothers' GP consultations were significantly more predictive of the child consultations for GI MUPS than those of fathers.

This current study also found significant dose-response relationship between duration of exposure to GP consultations for MUPS in the mother. This finding is consistent with the finding of a cross-sectional primary care study by Craig et al. (2002) who found a statistically significant association between the number of MUPS reported in the child and number of years the child has been exposed to a somatising parent.

7.5.3. Interpretation

There are several possible explanations for the observed associations between children exposure to maternal GP consultations for MUPS and similar consultations in children. A possible explanation for this is genetic predisposition to MUPS. There is some evidence that genetic effects contribute to the onset of some MUPS and syndromes, such as headache and IBS (Larsson et al., 1995, Morris-Yates et al., 1998). However, it seems that genetic predisposition to MUPS hypothesis is unlikely to entirely explain the findings of this study. This is because one would expect this association to be also significant for father-child pairs if genetic factors were the only factors underlying this association.

Another possible explanation for these findings is childhood social learning of illness behaviour, which has been hypothesised to play an important role in the development of illness and healthcare seeking behaviour for MUPS and functional somatic syndromes among children (Craig et al., 2002, Levy et al., 2007, Cardol et al., 2007, Levy et al., 2000). Previous research suggests that children learn their illness behaviour and healthcare seeking behaviour within the family. One of the models that have been proposed to explain family similarity in illness and health seeking behaviour is the Household Production of Health (HHPH) (Berman et al., 1994), which has been tested empirically by Cardol and colleagues (Cardol et al., 2005) in order to explain childhood learning of illness behaviour. They found that 22% of the variance in frequency of primary care consultations between patients can be attributed to family influence, which suggest an increased within-family similarity in consultation patterns. The similarity in consultation patterns within families has been hypothesised to occur due to shared circumstances (such as

living environment and family income), socialisation (e.g. process of learning health beliefs and attitudes), and similarity in background characteristics, such as vulnerability to illness and responses to stress (Cardol et al., 2005). Several studies have provided evidence for the validity of concepts within the HHPH model. A number of studies have suggested that parental responses and attitudes toward the child illness (reinforcement) and parental coping mechanisms with their own health complaints (role modelling) may influence symptoms frequency, disability days, and healthcare consultations in their children when they become adults (Whitehead et al., 1994, Walker & Zeman, 1992). For example, the study by Whitehead and his colleagues (1994) has shown that women with IBS were more likely than women without IBS to emulate the illness behaviour of their parents and to recall that their parents reinforced illness behaviour by rewarding them with special privileges, such as excluding them from household tasks, special care, or treat foods during their childhood. Protective parental responses to pain in their children were found to play an important role in pain catastrophising in adolescents with chronic musculoskeletal pain (Guite et al., 2011). Another study found that families who consulted a GP for abdominal pain in their children had greater worries and beliefs scores about abdominal pain than families who did not consult for their children with abdominal pain (van Tilburg et al., 2009).

This research was not designed to address the mechanisms underlying the social learning of illness behaviour in children exposed to parental consultations for MUPS. However, the findings of this study provide more support to the social learning of illness behaviour hypothesis by showing that children previously exposed to maternal GP consultations for MUPS were at increased odds of consulting for MUPS than unexposed children, which can be regarded as a proxy

measure for maternal beliefs and attitudes towards the GP consultation for MUPS (Newacheck & Halfon, 1986).

In this study, children exposed to GP consultations for MUPS in both parents had increased odds of GP consultations for MUPS, but this association was not significant for father-child pairs. These findings suggest that childhood exposure to maternal GP consultations for MUPS has a unique influence on the child GP consultations for MUPS. This also accords with the findings of previous work which found a dominant influence for maternal illness and healthcare seeking behaviour on the illness and healthcare seeking behaviour of their children (Cardol et al., 2006a, Cardol et al., 2005, Walker & Zeman, 1992, Campion & Gabriel, 1985).

These findings raise important questions about why and how illness and healthcare seeking behaviour of mothers have greater impact than that of fathers on the children illness and health seeking behaviour. Traditionally, mothers are responsible for raising children and usually spend more time with them, especially in the case of single mothers and young children. Therefore, the mother might be the first person to notice or perceive symptoms in her child and then decide whether to seek healthcare for the child or not (Campbell & Roland, 1996). Thus, the mother models for her child how to interpret and perceive symptoms of ill health and when to seek health care (Moran & O'Hara, 2006). In support for these statements, some studies have shown that maternal health care use is a significant predictor of child's health seeking behaviour (Ward & Pratt, 1996, Schor et al., 1987). For example, Schor and colleagues (1987) examined primary care consultations for family members for six consecutive years and found that

maternal influence on the child consultation was two to three times greater than paternal influence. Another study showed that mother's protective responses to child's abdominal pain were significantly associated with subsequent GP consultations for GI symptoms among children (Walker et al., 2006). Also, maternal protective responses during childhood were independently associated with the diagnosis of chronic fatigue syndrome in adulthood (Fisher & Chalder, 2003). Additionally, only maternal fears about abdominal pain differentiated children with abdominal pain who consulted a GP from those children with the same pain but did not consult (Venepalli et al., 2006).

GP consultation in children may reflect parental decision to consult for their children, and parents usually, especially in the case of young children, present the child's health complaints to the GP. Thus, it has been suggested that similarity in consultation patterns for MUPS between parents and children might be explained by parental biased perception of symptoms in their children that they have themselves rather than the child health status or need (Levy et al., 2000, Cardol et al., 2006b). However, in the current study, no significant effect of interaction was found between the child age group and maternal GP consultation for MUPS on the child GP consultation for MUPS, which indicate that the effect of maternal consultation for MUPS is similar across child age group. This suggests that maternal biased perception of MUPS in their children is unlikely to explain these observed associations. Also, this concern has been addressed in a previous study which found that children of mothers with IBS who consulted with GI MUPS made more primary care consultations for both GI and non-GI MUPS (Levy et al., 2004), which imply that the influence of maternal GP consultations for IBS related

symptoms is not specific to GI MUPS in their children, but also extends to other types of MUPS.

7.5.4. Strengths of the study

One of the main strengths of this study was that it included a large number of children and their parents registered with 12 GP practices, and therefore the findings are more likely to be generalisable to children and parents consulting in other practices of similar characteristics to those of CiPCA practices' populations.

One advantage of this study was that it used documented GP consultations, which is a more precise source of information on attendance in primary care than relying on self-reported data by children or their parents that may be prone to recall bias as the recall time is lengthened (Jordan et al., 2006a, Roberts et al., 1996, Bellon et al., 2000). Also, this research was performed using the CiPCA database which is a high quality database (see section 5.2.1.).

Another advantage of this study was that it included children from all age groups and used a broad list of MUPS, which allowed a comprehensive examination of the whole spectrum of MUPS experienced by parents and children across age groups. Studies focusing on specific MUPS in certain age groups can be important but they may not identify children at risk of developing other MUPS at different ages.

Also, to minimise the possible variability of coding consultations for MUPS between GPs or practices, a comprehensive list of all possible diagnostic and symptoms Read codes that might be used by the GPs to record consultations for

MUPS were included. A practicing GP was involved in selection of the list of Read codes. Moreover, “free-text” consultation records for all coded consultations for MUPS were examined in detail to identify consultations that were, in the opinion of the GP, for MUPS. To avoid any bias in classifying explained physical symptoms and MUPS, this process was carried out separately for children and their parents before merging their GP consultation data.

7.5.5. Limitations of the study

This research has used the CiPCA database, which is an anonymised primary care database, and identification of potential parents of index children was based on full address details and surnames for practice registered populations. Although this study was not designed to investigate genetic predisposition to MUPS, it was not possible to establish whether the persons that were defined as parents were the biological parents for selected children or not by using data available from the CiPCA database, which weaken interpretation of findings with respect to the possible role of genetic predisposition to MUPS. Nevertheless, family members usually register with the same GP practice (Simon, 2008). Additionally, the household structure for the CiPCA households for selected children were almost identical to structure of households with children in UK using data from Office for National Statistics on live births by age group of mother and father at birth of the baby, percentages of number of children in the family, and age group of the youngest child in the household (see sections 5.2.1 to 5.2.2). Moreover, to reduce the possibility of errors in identification of parents of selected children, all

households with more than one member meeting the definition of a parent as used in this research were excluded.

The fathers of large proportions of children (41.3%) were not identified. This was because fathers were registered with other practices or were not registered with any practice, or because children were living with single-mothers. So, exposure status for paternal GP consultations for MUPS for a considerable proportion of children was unknown. It is unlikely that the lack of significant associations between child exposure to paternal consultations for MUPS and child consultation for MUPS is entirely attributed to low statistical power as the numbers of children with paternal consultation data were more than those needed based on sample size calculations (see section 7.3.5). However, the potential for bias due to missing of paternal GP consultations data for considerable proportions of children remains a possible explanation.

Another limitation for this study is the potential for diagnostic misclassification, which is a common problem in primary care (de Lusignan, 2005). However, as discussed in pervious chapter (section 6.5.4), diagnostic misclassification is unlikely to completely explain the associations found in this study due to the high quality of coded clinical data within CiPCA practices. Also, documented patient's attendance at general practice is more likely to be complete as it is a legal requirement for all GP practices in the UK. Additionally, the current classification system used in primary care allows for coding definitive diagnoses as well as symptoms, which reduces the potential for diagnostic misclassification. Another potential source of misclassification bias may have occurred if children who

consulted for MUPS that were not coded as their chief complaint, if they had more than one reason for consultation.

Another disadvantage is that this study was not able to measure some factors that might be associated with GP consultations for MUPS in children, such as ethnicity and severity of MUPS. However, this is unlikely to change the conclusions drawn from this study. Ethnicity was measured in some studies and was not found significantly associated with GP consultations for MUPS in parents and children (Little et al., 2001, Boey & Goh, 2001c, Boey & Goh, 2001a). In this study, the results remained significant after adjusting for the most important factors associated with child GP consultations for MUPS including frequency of GP consultations.

7.5.6. Generalisability

Over 97% of the UK population is registered with GP practices (Department of Health, 2011). The primary care consultation data used in this study was drawn from 12 GP practices of registered populations of over 100000 persons from North Staffordshire. Thus, the findings of this study are more likely to reflect the consultation patterns for MUPS in these populations. As stated in previous chapter (section 6.5.4), North Staffordshire area is more deprived than England as a whole. But this is unlikely to limit the generalisability of these findings to other areas in England or the UK. This is because there were no statistically significant associations between the child GP consultation for MUPS and area level deprivation in both univariable and multivariable analyses.

Also, although this study set out to examine consultation patterns for MUPS between parents and children in primary care, recorded primary care consultations data only provide a measure of health problems for which practice registered populations have consulted. Thus, primary care consultations data might underestimate the occurrence of MUPS in parents and children in the general population, especially in the case of minor MUPS of short duration, for which the decision to consult might be influenced by patients' health beliefs and attitudes to health care (Campbell & Roland, 1996).

7.5.7. Implication for clinical practice and future research

This study has demonstrated that children who were previously exposed to maternal GP consultations for MUPS were at increased odds of GP consultations for MUPS as compared to unexposed children. This association was strengthened by evidence of increasing odds of GP consultations for MUPS in children with increasing levels of dose intensity of exposure to GP consultations for MUPS in their mothers. Childhood learning of illness behaviour is one of the plausible explanations for these findings. The impact of maternal GP consultations for MUPS on the health and GP consultations of their children has implications for the management of parents and children presenting with MUPS in primary care. It is important that GPs be aware of this link as such insights might direct the GP toward alternative management approaches. Recognising similarity in consultation patterns for MUPS within families, especially frequent attending families, provides a rationale for the GP to respond differently and attempt to modify any inappropriate illness and consulting behaviour clustering within such families.

So far, however, there has been very little research on the most appropriate interventions that can be used to modify illness and healthcare seeking behaviour of parents and their children. Nonetheless, a recent randomised controlled study has demonstrated that cognitive behaviour therapy (CBT) targeting children's coping responses to recurrent abdominal pain and parents' responses to pain in their children was associated with significant reduction in pain and other gastrointestinal symptoms severity in children in the CBT group than children in the comparison group at 1 week, three months, and six months follow-up (Levy et al., 2010). Also, parents of children in the CBT group reported greater decreases in their protective responses to pain in their children as compared to parents of children in the comparison group at the same points of follow-up. Preliminary findings from another randomised controlled trial showed that CBT for children presenting in primary care and speciality clinics with persistent functional somatic symptoms and anxiety was associated with significant improvements in anxiety symptoms and reduction in pain severity and discomfort due to GI symptoms after treatment and at three months of follow-up compared to controls (Warner et al., 2011). These findings appear to be promising in the management of children presenting with MUPS. Therefore, more studies with longer periods of follow up are needed. However, these trials did not measure children's consultations patterns for MUPS before and after CBT. So, it is not clear whether CBT had an impact on the consultation behaviour of children for MUPS. But, there is some evidence from literature on adults that CBT and pharmacological therapy for patients presenting with non-specific MUPS in primary care and general outpatient clinics are effective in reducing frequency of symptoms, the number of consultations, and psychological distress (Husain et al., 2007, Sumathipala et al.,

2000, Speckens et al., 1995). Also, a randomised controlled trial in the UK showed that aerobic exercise training for primary care patients presenting with MUPS is effective in reducing number of consultations and prescriptions (Peters et al., 2002). Potentially, such interventions for parents could impact on the illness and healthcare seeking behaviour of both parents and their children, but no studies exist to confirm or refute this. This provides a rationale for future research to focus on development of clinical guidelines on management of parents and children presenting with MUPS in primary care, including educational programmes for parents on how to respond to their MUPS as well as MUPS in their children. Additionally, more research is needed to better understand the exact mechanisms underlying social learning of illness behaviour, which might shed light on interventions that can be employed to help families adopt more appropriate illness and heath seeking behaviour that can be transmitted to next generations.

7.6. Conclusion

This study suggests that exposure to maternal GP consultations for MUPS is a significant risk factor for similar consultations in their children. This finding was strengthened by evidence of dose-response relationships indicating increases in odds of GP consultations for MUPS in children with increasing levels of dose intensity and duration of exposure to maternal GP consultations for MUPS. This study adds further evidence that children may learn their illness and GP consultation behaviour from their mothers and that recurrent presentation with MUPS in children should be viewed within a family context. It is important for

primary care practitioners to be aware of this link, who may wish to use alternative management approaches for these children.

Chapter 8. The association of GP consultations for specific MUPS between mothers and children: a case-control study

8.1. Introduction

This chapter presents the results of a case-control study investigating the associations between maternal and child GP consultations for MUPS classified by type (painful and not painful), body system, and anatomical site. This study includes 5417 child-mother pairs (1437 cases and 3980 controls). Following a description of the methods used in this study, baseline demographic and health related characteristics of children and their mothers are presented. Both univariable and multivariable analyses, investigating the associations with their corresponding ORs and 95% CIs, are then presented. A summary of the main findings, a comparison with previously published literature, an interpretation of the findings, and implications for clinical practice and future research are also presented.

8.2. Aims and objectives

The primary aim of this chapter is to investigate whether GP consultations for MUPS in children are associated with GP consultations for MUPS in their mothers, stratified by type of MUPS (painful and not-painful), different body systems, and specific MUPS (see sections 5.5 and 5.5.2). The specific objectives include investigating the following hypotheses:

(1) There is an association between GP consultations for painful and not-painful MUPS in mothers and children.

(2) There will be dose-response relationships between different levels of dose intensity of exposure to maternal GP consultations for painful and not-painful MUPS and similar consultations in the child.

(3) There is an association between GP consultations for MUPS according to body system in mothers and children.

(4) There is an association between GP consultations for specific MUPS in mothers and children.

8.3. Methods

Some methods that were used in the previous chapter (chapter 7) were also used in this chapter, including, setting; study period; case-control definitions and selection; data collection methods for demographic variables and potential effect modifiers, and sample size calculation. The following methods were specifically used in this study.

8.3.1. Design

This study[1] used an unmatched case-control approach. The numbers of cases with painful and not-painful MUPS, body system categories, and specific MUPS were anticipated to be relatively small in specific MUPS analyses, and thus

[1] This case-control study included extra 109 cases that were excluded from the previous study (chapter 7) due to lack of enough controls to match to.

numbers of controls will also be relatively small if we match controls to cases. Therefore, matching was not used and all available cases and controls were included.

8.3.2. Maternal consultations for MUPS

The main exposure of interest was maternal GP consultation for MUPS, sorted by painful and not-painful MUPS, body system, and specific MUPS. To examine hypothesis 8.2.1., GP consultation status (yes, no) for MUPS in mothers and children were grouped into two categories, painful and not-painful MUPS. To investigate hypothesis 8.2.3, two measure of dose intensity were used:

- The number of GP consultations for painful and not-painful MUPS in mothers in 2007 and 2008.
- The number of different painful and not-painful MUPS in mothers in 2007 and 2008.

To examine hypothesis 8.2.2., the status of GP consultation for MUPS in mothers and children (yes, no) were grouped under five body systems, including musculoskeletal, gastrointestinal, cardiopulmonary, urogenital, and neurological MUPS; see box 5.1 for more details.

To examine hypothesis 8.2.4, maternal and child GP consultations status for each individual MUPS was determined and coded as yes or no.

8.3.3. Statistical analysis

Descriptive statistics were used to describe the sociodemographic and health related characteristics of children and their mothers. Chi-squared tests were performed to test for significant baseline differences between cases and controls for categorical variables, and Mann-Whitney U tests were performed for continuous variables. Univariable analyses for the association between all variables and child GP consultations for MUPS were performed using the logistic regression procedure in SPSS. Multivariable models were then fitted to examine the association between GP consultations for MUPS in children and their mothers according to different body organ systems, painful and not-painful MUPS, and specific MUPS; and adjusted for potential effect modifiers and other variables that were significantly associated with child GP consultation for MUPS in the univariable analyses. Poisson regression models were performed to examine dose-response relationships using number of GP consultations for painful and not-painful and number of different painful and not-painful MUPS in mothers and children. The multivariable analysis included variables that were significant with a *p*-value of ≤0.25 in the univariable analyses (see section 7.3.7 for justification); variables were entered into the model simultaneously. All calculated *p*-values were two-sided and significance level was set at a *p*-value of ≤0.05. Associations were estimated and summarised using ORs with 95% CI. All analyses were carried out using SPSS for Windows (IBM Corp, 2011). To check for any effects of multicollinearity on adjusted ORs, correlation analyses were performed to examine the strength and direction of the linear relationship between independent variables, for more details about multicollinearity see section 7.4.

8.4. Results

8.4.1. Sociodemographic and health related characteristics of children and mothers

5417 (1437 cases and 3980 controls) child-mother pairs were included in the analysis. Baseline sociodemographic and health related characteristics of children and their mothers are summarised in table 8.1. Baseline differences between cases and controls were statistically significant for all variables except for gender and IMD quintiles (see table 8.1). Case children were slightly older than control children, with a mean age of 9.5 years and 8.3 years, respectively. Children aged 12-16 years were over represented (42.3%) in the case group as compared to the control group (29.6%). Also, children aged 5 years and under were over represented in the control group (42.4%) in comparison to the case group (33.6%).

The proportion of cases (58.6%) whose birth order was first was slightly higher than that for controls (52.3%). The proportion of cases from households of more than three members was lower (45.8%) compared to controls (52.1%).

16.1% of cases were frequent consulters, whereas only 5.1% of controls were frequent consulters.

Cases had a higher proportion (25.3%) of maternal history of anxiety or depressive disorders between 2007 and 2008 than controls (19.9%).

Table 8.1. Baseline sociodemographic and health related characteristics of children and mothers

Variable	Cases (n=1437)	Controls (n=3980)	p-value
Child age[a,b]	9.5 (4.7)	8.3 (4.5)	<0.001
Child age group			
2-6 years	483 (33.6%)	1688 (42.4%)	<0.001
7-11 years	346 (24.1%)	1114 (28.0%)	
12-16 years	608 (42.3%)	1178 (29.6%)	
Female	790 (55.0%)	2073 (52.1%)	0.060
Mother age	37.7 (7.8)	36.7 (7.3)	<0.001
Mother age group 2009			
19-29 years	249 (17.4%)	722 (18.1%)	<0.001
30-40 years	646 (45.0%)	1972 (49.5%)	
41-51 years	497 (34.6%)	1227 (30.8%)	
52-62 years	43 (3.0%)	59 (1.5%)	
Child birth order			
First	842 (58.6%)	2083 (52.3%)	<0.001
Not first	595 (41.4%)	1897 (47.7%)	
Household members' count			
≤3	779 (54.2%)	1908 (47.9%)	<0.001
>3	658 (45.8%)	2072 (52.1%)	
IMD 2007quartiles			
I	306 (21.3%)	819 (20.6%)	
II	280 (19.5%)	785 (19.7%)	0.511
III	297 (20.7%)	792 (19.9%)	
IV	301 (20.9%)	809 (20.3%)	
V	244 (17.0%)	759 (19.1%)	
Missing IMD score	9 (0.6%)	16 (0.4%)	
Child GP consultation frequency			
Frequent consulters	232 (16.1%)	211 (5.3%)	<0.001
Non-frequent consulters	1205 (83.9%)	3769 (94.7%)	
Mother history of anxiety or depressive disorder			
Yes	364 (25.3%)	792 (19.9%)	
No	1073 (74.7%)	3188 (80.1%)	<0.001

[a] Data are means (SD) or numbers (%); [b] Percentages may not total 100 due to rounding

8.4.2. The association between GP consultations for painful and not-painful MUPS in mothers and children

The first analysis examined the association between GP consultations for painful MUPS in mothers and children (959 cases and 3980 controls). Univariable and multivariable analyses showed significant associations between GP

consultations for painful MUPS in mothers and children; crude OR 1.56, 95% CI 1.35 to 1.81 and adjusted OR 1.43, 95% CI 1.23 to 1.67.

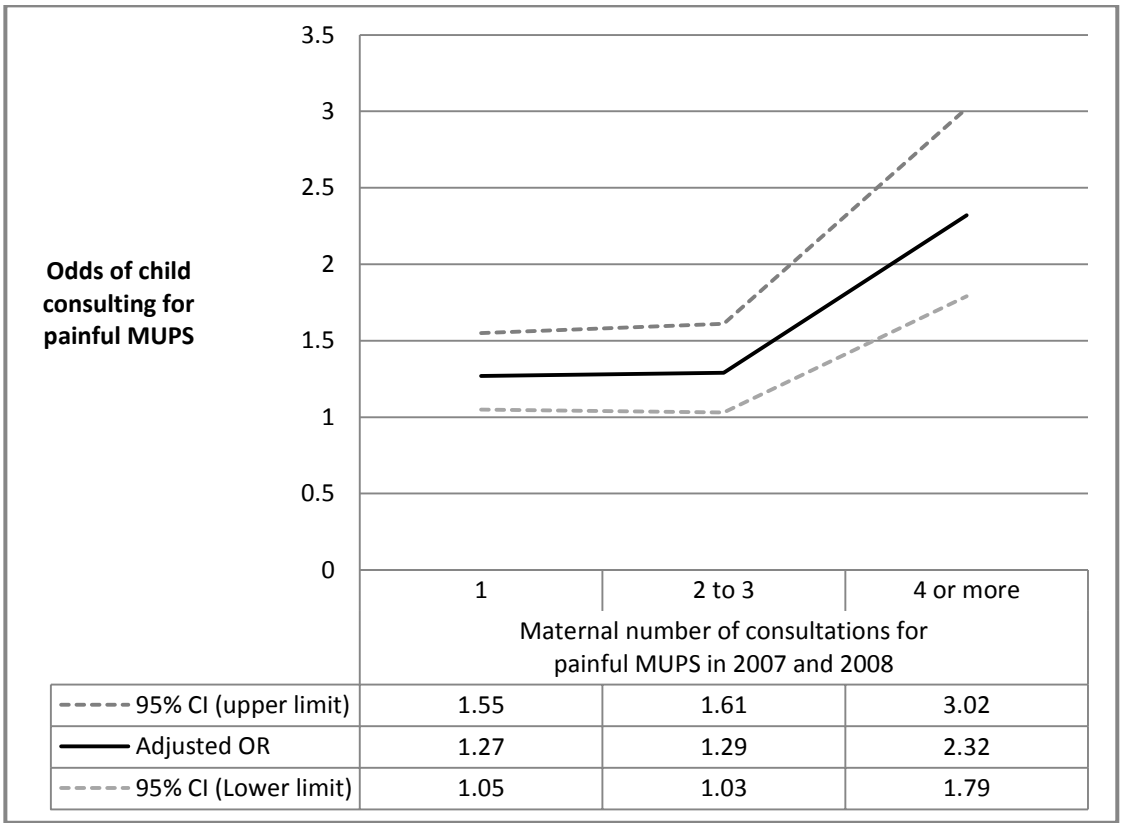
The second analysis examined the association between GP consultations for not-painful MUPS in mothers and children (581 cases and 3980 controls).This association was statistically significant in the univariable analysis (crude OR 1.31, 95% CI 1.05 to 1.62). However, this association was not statistically significant after adjusting for other covariates (adjusted OR 1.15, 95% CI 0.91 to 1.44).

In the multivariable analyses above, ORs were adjusted child age group, child gender, mother age group, child birth order, household members count, IMD 2007, practice, mother psychiatric history, and child consultation frequency.

8.4.3. Dose –response associations between GP consultations for painful MUPS in mothers and children

Poisson regression analyses found statistically significant associations between the number of GP consultations for painful MUPS in mothers and children (959 cases and 3980 controls). An increase of 1 maternal GP consultation for painful MUPS was associated with 7% higher rate of GP consultation for painful MUPS in the child (crude OR 1.11, 95% CI 1.09 to 1.13; adjusted OR 1.07, 95% CI 1.05 to 1.10). Logistic regression analyses demonstrated that an increase in the number of maternal GP consultations for painful MUPS was associated with increased odds of child consultation for painful MUPS (see figure 8.1).

Figure 8.1. The association between maternal number of consultations for painful MUPS and child consultation status for painful MUPS

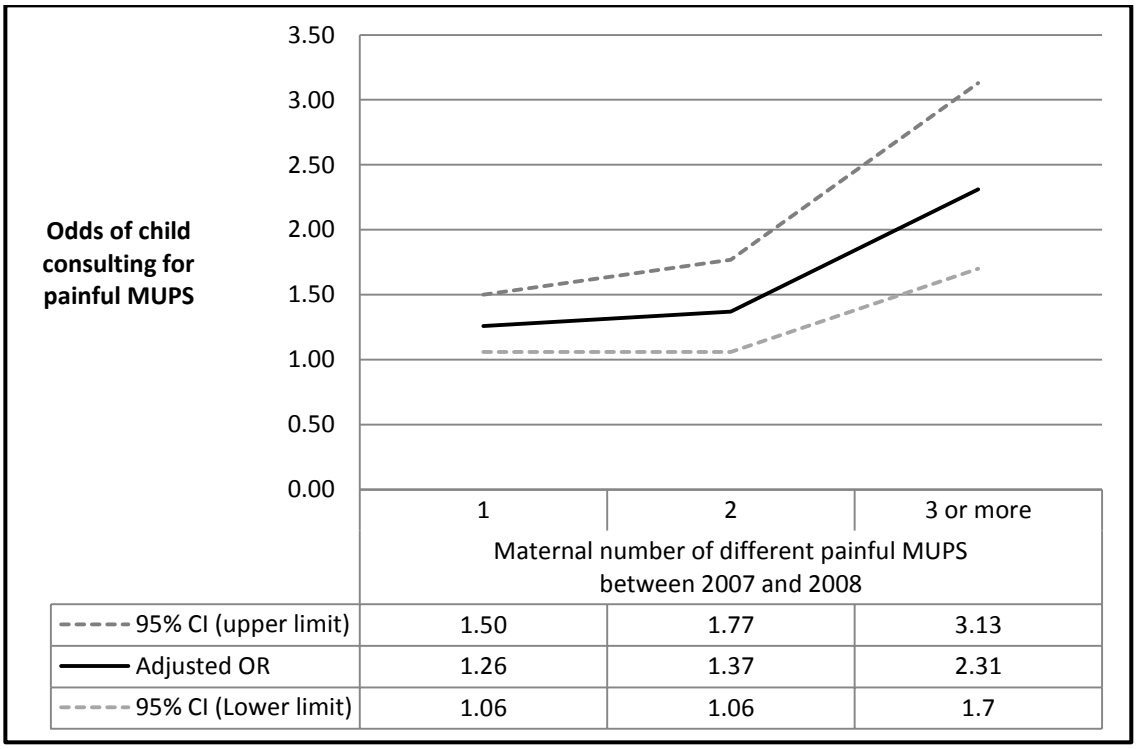


	1	2 to 3	4 or more
95% CI (upper limit)	1.55	1.61	3.02
Adjusted OR	1.27	1.29	2.32
95% CI (Lower limit)	1.05	1.03	1.79

ORs were adjusted for child age group, child gender, mother age group, child birth order, household members count, mother psychiatric history, and child consultation frequency.

Similarly, Poisson regression analyses indicated significant associations between numbers of different painful MUPS in mothers and children. An increase of 1 maternal painful MUPS was associated with 16% higher rate of GP consultation for painful MUPS in children (crude OR 1.24, 95% CI 1.18 to 1.30; adjusted OR 1.16, 95% CI 1.10 to 1.22). Also, logistic regression analyses indicated statistically significant associations between numbers of different painful MUPS in mothers and increased odds of child GP consultation for painful MUPS (see figure 8.2).

Figure 8.2. The association between maternal number of painful MUPS and child consultation status for painful MUPS



	1	2	3 or more
95% CI (upper limit)	1.50	1.77	3.13
Adjusted OR	1.26	1.37	2.31
95% CI (Lower limit)	1.06	1.06	1.7

ORs were adjusted for child age group, child gender, mother age group, child birth order, household members count, mother psychiatric history, and child consultation frequency.

To examine the association between GP consultations for multiple pain sites between mothers and children, the analysis was restricted to cases (n= 95) who had consulted with 2 or more different MUPS and controls (n= 3980). This analysis found that maternal consultation for multiple (2 or more) painful MUPS was associated with increased odds of child consultation for multiple painful MUPS (crude OR 5.01, 95% CI 2.89 to 8.69; adjusted OR 3.35, 95% CI 1.77 to 6.36).

8.4.4. Associations between GP consultations for MUPS in mothers and children according to body system

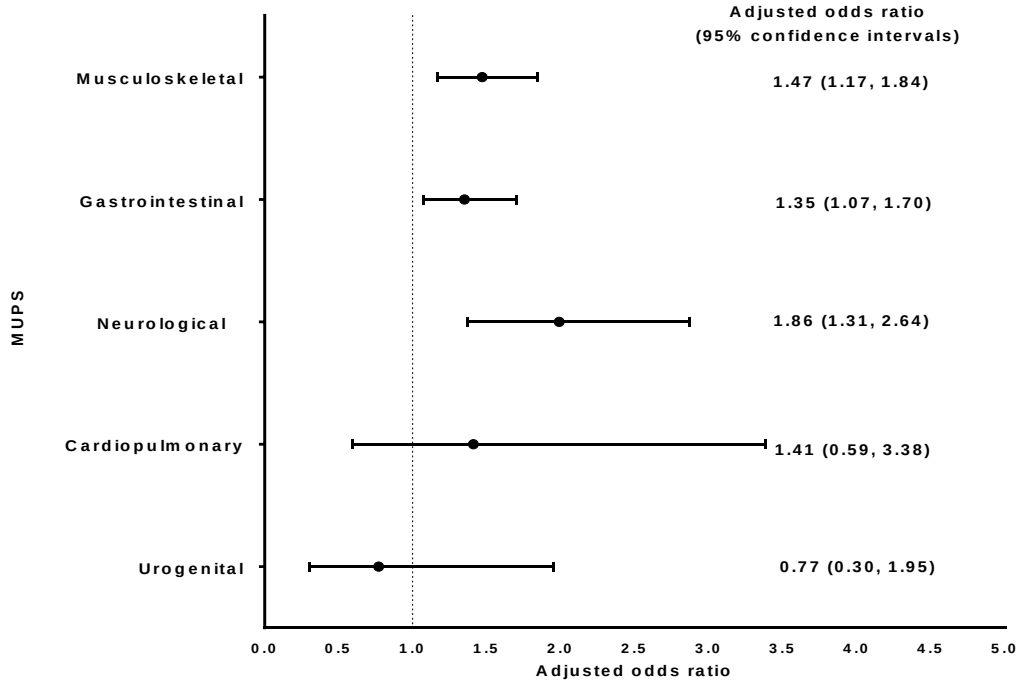
Table 8.2 presents the crude ORs for the associations between GP consultations for MUPS in mothers and children according to body system. Univariable logistic regression analyses showed statistically significant associations (OR >1) between maternal GP consultations for musculoskeletal, gastrointestinal, and neurological MUPS and similar GP consultations in children (see table 8.2). No statistically significant associations were found between GP consultations for urological and cardiopulmonary MUPS in mother and children. However, these analyses were based on small numbers of available cases and the 95% CIs are wide (e.g. crude OR for cardiopulmonary MUPS was 1.87, 95% CI 0.80 to 4.36); see table 8.2.

Table 8.2. The association between GP consultations for MUPS according to body system in mothers and children

Mother consultation status	Cases (n)	Controls (n)	Crude ORs (95% CI)
Musculoskeletal MUPS			
No	508	3121	
Yes	139	859	1.64 (1.32 to 2.03)
Gastrointestinal MUPS			
No	580	3503	
Yes	121	477	1.53 (1.23 to 1.91)
Neurological MUPS			
No	198	3568	
Yes	45	412	1.97 (1.40 to 2.76)
Urogenital MUPS			
No	80	3729	
Yes	5	251	0.93 (0.37 to 2.31)
Cardiopulmonary MUPS			
No	78	3823	
Yes	6	157	1.87 (0.80 to 4.36)

After adjusting for all statistically significant covariates, associations between maternal and child GP consultations for musculoskeletal, gastrointestinal, and neurological MUPS remained statistically significant, see figure 8.3.

Figure 8.3. The association between GP consultations for MUPS according to body system in mothers and children



ORs were adjusted for GP practice, child gender, child age group, mother age group, child birth order, household members count, mother psychiatric history, and child consultation frequency.

8.4.5. The association between GP consultations for specific MUPS in mothers and children

Examining the associations between GP consultations for specific MUPS in mothers and children was performed only for the top 10 most common MUPS in children (data not shown). These 10 MUPS were: abdominal pain, joint pain,

headache, back pain, fatigue, pain in extremities, constipation, fainting or dizziness, diarrhoea, and vomiting.

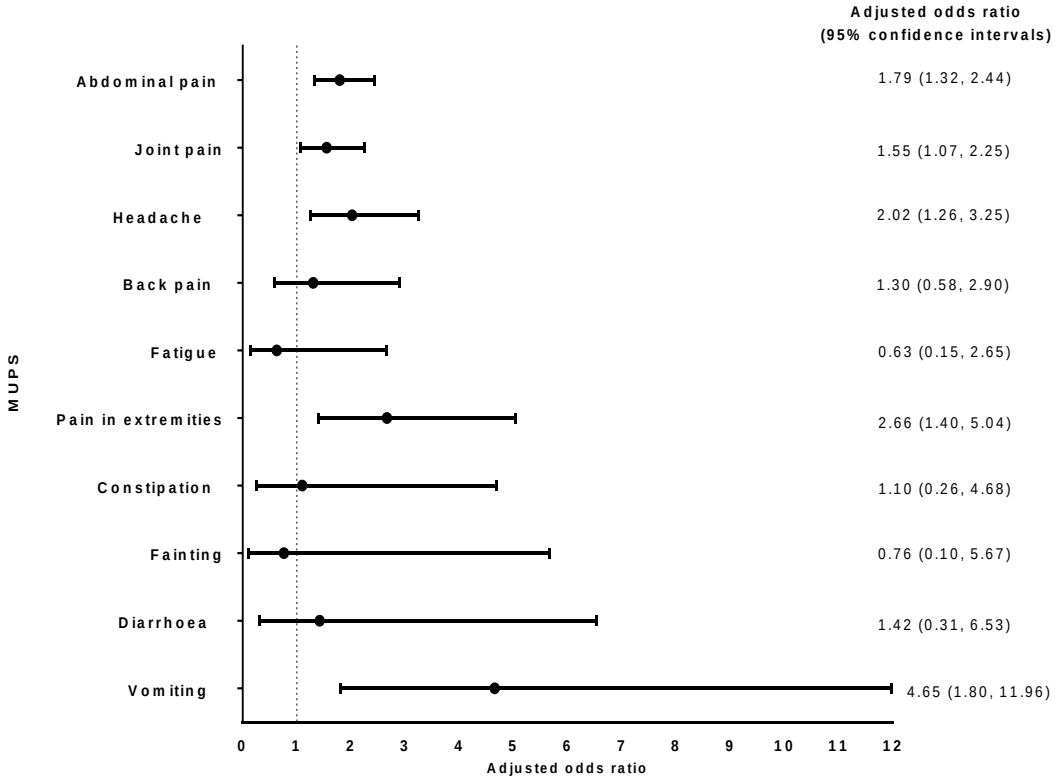
In univariable logistic regression analyses, statistically significant association were found between maternal and child GP consultation for 5 MUPS (abdominal pain, joint pain, pain in extremities, headache, and vomiting). Crude ORs with 95% CIs are presented in table 8.3.

Table 8.3. The associations between GP consultation for specific MUPS in mothers and children

	MUPS in the child		
MUPS in the mother	**Yes**	**No**	**Crude ORs (95% CI)**
Abdominal pain			
Yes	64	345	2.13 (1.60 to 2.85)
No	316	3635	
Joint pain			
Yes	39	428	1.70 (1.19 to 2.44)
No	190	3552	
Headache			
Yes	24	284	2.03 (1.30 to 3.17)
No	154	3696	
Vomiting			
Yes	6	26	6.00 (2.44 to 14.80)
No	152	3954	
Constipation			
Yes	2	46	1.19 (0.29 to 4.94)
No	144	3934	
Pain in extremities			
Yes	12	164	2.91 (1.56 to 5.41)
No	96	3816	
Diarrhoea			
Yes	2	42	2.08 (0.50 to 8.70)
No	90	3938	
Fatigue			
Yes	2	167	0.66 (0.16 to 2.72)
No	69	3813	
Back pain			
Yes	8	309	1.79 (0.85 to 3.81)
No	53	3671	
Fainting or dizziness			
Yes	1	104	0.65 (0.09 to 4.77)
No	57	3876	

After adjusting for significant covariates, associations between maternal and child GP consultations for the above stated MUPS remained statistically significant. Figure 8.4 presents adjusted ORs with 95% CIs for the associations.

Figure 8.4. The associations between GP consultation for specific MUPS in mothers and children



ORs were adjusted for GP practice, child gender, child age group, mother age group, child birth order, household members count, mother psychiatric history, and child consultation frequency.

8.5. Discussion

8.5.1. Summary of main findings

As hypothesised, the results of these analyses found statistically significant associations between GP consultations for painful MUPS in mothers and children, with evidence of dose-response relationships for the number of consultations for painful MUPS and the number of painful MUPS including multiple pain sites. The current study found significant associations between GP consultations for MUPS grouped according to body systems in mothers and children, including musculoskeletal, gastrointestinal, and neurological MUPS. Additionally, statistically significant associations between GP consultations for the following MUPS in mothers and children were found: abdominal pain, vomiting, joint pain, pain in extremities, and headache. It is interesting to note that four of these MUPS are painful MUPS.

The current study found no statistically significant association between GP consultations for not-painful MUPS in mothers and children.

8.5.2. Comparison with existing literature

The findings of this study with respect to the association between GP consultations for MUPS or body systems in mothers and children are consistent with the findings of previous studies that examined this association for specific MUPS only (Levy et al., 2000, Levy et al., 2004, Cardol et al., 2006b); see table 4.2 and section 4.4.4. For example, Cardol and colleagues found an association

between GP consultations for abdominal pain and headache in parents and children.

The findings of this study are also in agreement with other population-based studies that only examined the association between self-reports of specific MUPS (without GP consultation data) in parents and children. A few studies have reported relationships between history of headache or migraine in parents and children (Kroner-Herwig et al., 2007, Laurell et al., 2005, Aromaa et al., 1998). One study found a link between history of Juvenile Primary Fibromyalgia Syndrome in adolescents and their parents (Schanberg et al., 1998). Another study found a relationship between history of back pain and headache in mothers and their children, including multiple painful symptoms (Saunders et al., 2007). In the above mentioned study, children who reported two or more painful MUPS in the last 6 months had higher odds of having their mother reporting two painful MUPS (adjusted OR 1.9, 95% CI 1.4 to 2.6) and three or more painful MUPS (adjusted OR 2.4, 95% CI 1.8 to 3.1) in the same period as compared to controls. These ORs are very comparable in magnitude to the ORs obtained in the current study (see figure 8.2).

In this chapter, a statistically significant association was found between maternal GP consultations for vomiting in 2007 and 2008 and child GP consultations for vomiting in 2009. As far as the author is aware, none of the existing published studies has specifically investigated this association. Only six children who consulted for vomiting in 2009 also had their mothers consulted for vomiting in 2007 and 2008. The reason for this association is not clear. The GP consultation records in 2009 for the mothers of these six children were reviewed

and showed that they did not consult for vomiting in 2009. This suggests that this association is not likely to be a link to an infection in the mother and the child. However, the mothers and their children had a consultation history for abdominal pain that can be related to vomiting, which may explain this association.

8.5.3. Interpretation

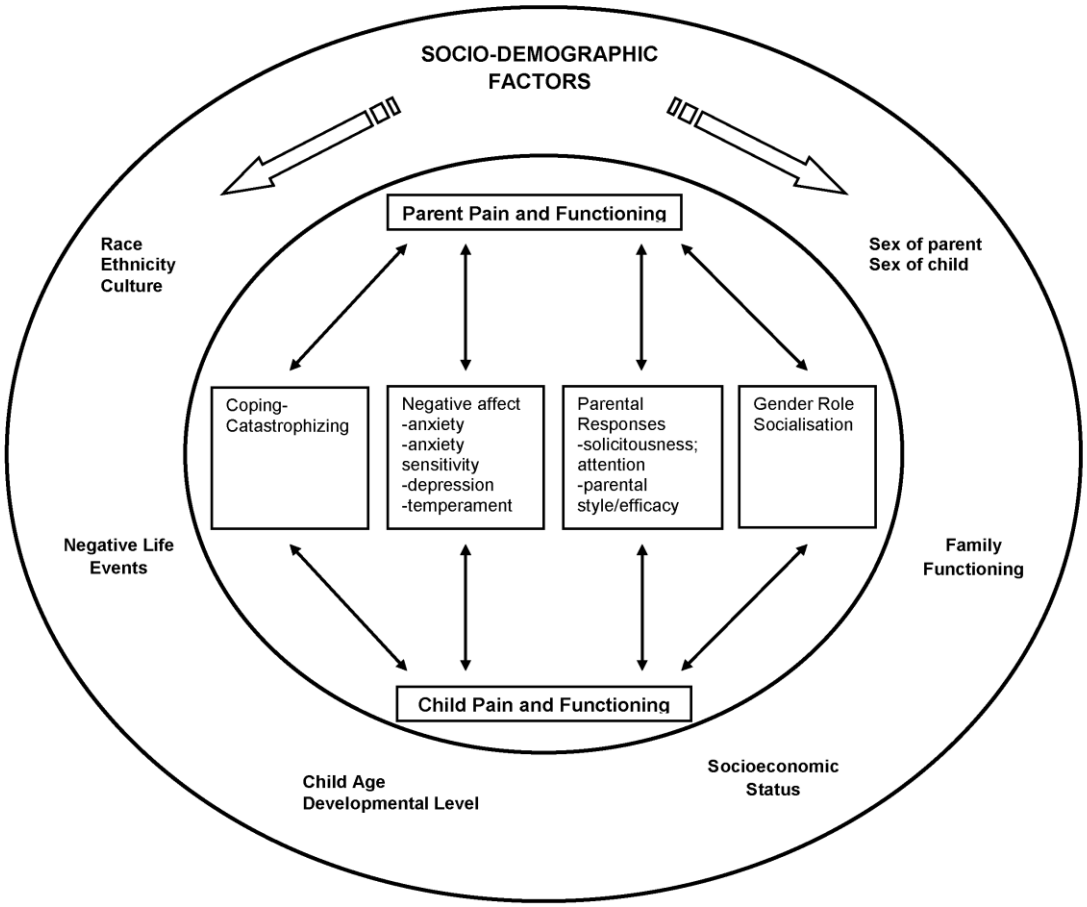
As discussed in chapter 7, there are several possible explanations for the observed associations between GP consultations for MUPS in mothers and children, including genetic predisposition and childhood social learning of illness behaviour (see section 7.5.3).

The results of genetic studies have demonstrated that both genetic and environmental factors influence the occurrence of MUPS and functional somatic syndromes, such as headache (Larsson et al., 1995, Kato et al., 2009), IBS (Morris-Yates et al., 1998, Kato et al., 2009, Levy et al., 2001), LBP (El-Metwally et al., 2008), fatigue (Kato et al., 2009, Fowler et al., 2006), and widespread pain(Kato et al., 2009).

The findings of this chapter also provide support to the childhood social learning of illness behaviour hypothesis by showing that the association of GP consultations of MUPS between mother and children is mostly significant for painful MUPS, which extend to specific associations for the majority of painful MUPS. This suggests that maternal modelling of illness behaviour for painful MUPS and attitudes towards childhood pain (reinforcement) are plausible explanations for these findings. Additionally, these findings (mother-child pain

relationship) agree with some conceptual models suggesting that biological, psychological, and socio-demographic factors play an important role in the parent-child pain relationships (Evans et al., 2008, Palermo & Chambers, 2005). Figure 8.5 presents Evans and colleagues' (2008) conceptual model which links parental and child pain.

Figure 8.5. Conceptual model linking parental and child pain



Source: adapted from Evans et al (2008, p.12)

This study found only significant association between GP consultations for painful MUPS in mothers and children. This association was statistically significant for abdominal pain, headache, joint pain, pain in extremities, but not for back pain.

The OR for the association between GP consultation for back pain in mothers and children was 1.23, but this was not statistically significant (CI 0.57 to 2.65). This OR was obtained based on relatively small number of children who consulted for back pain (n= 61). Therefore, the lack of statistically significant association between GP consultations for back pain in mothers and children may be explained by a lack statistical power to detect an association, and does not imply that this association does not exist at all.

This study also found no statistically significant association between GP consultations for specific not-painful MUPS in mothers and children, including fainting or dizziness, fatigue, constipation, and diarrhoea. This also could be attributed to low statistical power because the analyses of these symptoms were based on small number of children (see table 8.3). However, the association between GP consultations for not-painful MUPS in mothers and children was also not statistically significant even after including all children who consulted for not-painful MUPS in one group (n=581). Therefore, it is unlikely that a lack of statistical power can explain the absence of a statistically significant association between GP consultations for not-painful MUPS in mothers and children.

One important point is that the lack of statistically significant associations between GP consultations for back pain and not-painful MUPS in mothers and children does not suggest that these associations do not exist in the general population. These findings only apply to MUPS for which parents and children have consulted for. Therefore, these findings do not contradict the findings of other population-based studies which reported significant associations for MUPS (such

as back pain, fatigue, nausea, diarrhoea, fainting) between parents and children using self-report data.

Another important point with respect to the observed associations between GP consultations for painful MUPS, but not for not-painful MUPS, is that these associations might be explained by the variation in the occurrence and GP consultation rates for these MUPS. In this study mothers and children consulted more for painful MUPS than for not-painful MUPS (see table 8.3). Also in the descriptive epidemiologic study, presented in chapter 6, children consulted more often for painful MUPS than not-painful MUPS (see table 6.2). This seems to be a plausible explanation and accords with the findings of other studies. For example, in a study from The Netherlands, the parents of 1805 children completed a health diary about GP consultations for MUPS in their children over three weeks (Bruijnzeels et al., 1998). This study showed that only 20% of children with symptoms consulted a GP during the three weeks period. In the same study, 13% of children consulted for musculoskeletal pain, whereas only 2% and 1% of children consulted for nausea and fatigue during the same period, respectively.

The above mentioned explanation raises the question of why people consult for painful MUPS more often than not-painful MUPS. The literature suggests that GP consulting behaviour in both adults and children is influenced by level of pain severity and perceived seriousness of the symptoms. Pain intensity and related functional disability were reported as significant predictors of GP consultations for chronic benign pain (continuous or recurrence pain for three months) (Perquin et al., 2000b, Perquin et al., 2001), non-specific musculoskeletal pain (Masiero et al., 2010), and abdominal pain (Boey & Goh, 2001a) in children. So, probably parents

perceive painful MUPS in themselves and in their children as more serious than not-painful MUPS, which influence their GP consultation rates for these MUPS.

8.5.4. Strengths and limitations of the study

This study included large numbers of mothers and children and was able to examine the association between GP consultations for MUPS by categorising MUPS in mothers and children according to type, body system, and anatomical site. Moreover, the significant associations between GP consultations for painful MUPS in mothers and children were strengthened by evidence of dose-response relationships using different levels of dose intensity representing the “magnitude or frequency” of child exposure to maternal GP consultations painful MUPS and subsequent similar consultations in the child.

In addition to the limitations of discussed in previous chapter which are related more generally to the study design and potential biases, some analyses which examined the association between GP consultations for some specific MUPS in mothers and children were based on small number of children. Therefore, the lack of statistically significant association for some MUPS might be due to low statistical power. Another limitation is that the findings of this study do not reflect the occurrence of MUPS in the general population. However, these findings are more generalisable to mothers and children consulting for MUPS in primary care

8.5.5. Implication for clinical practice and future research

This study has shown that children who were previously exposed to maternal GP consultations for painful MUPS were at increased odds of GP consultations for painful MUPS, with evidence for dose-response relationships. This study has also identified specific body systems and body sites in which this association becomes more apparent. In addition to the implications for clinical practice and future research discussed in the previous chapter (section 7.6.6).

The results of this study also signify the importance of raising the awareness of GPs that consultation for painful MUPS in children might be linked to current or previous GP consultations for painful MUPS in their mothers, and that GP consultations for painful MUPS in children should be viewed within a family context.

These findings further support to the idea that future research should examine parent-child pain relationships using a comprehensive model that incorporate both biological and psychosocial factors (Evans et al., 2008). Such research may delineate the exact parental factors that contribute to development of pain and related consulting behaviour among children. This has implications for designing more appropriate interventions, which encompass family factors and involve parents in the management of their children presenting with MUPS in primary care.

8.6. Conclusion

This study showed that maternal GP consultation for painful MUPS is a significant risk factor for similar GP consultations in their children. This finding was strengthened by evidence of dose-response relationships showing progressive increase in numbers of painful MUPS and related GP consultations in children with increasing levels of dose intensity of exposure to number of painful MUPS and related GP consultations in their mothers. Additionally, this study found significant associations between child exposures to maternal consultations for most common painful MUPS sorted by body system and anatomical site and consequent similar GP consultations in their children. These results add further evidence supporting the childhood social learning of illness and consulting behaviour hypothesis. GPs need to be aware that maternal illness and GP consultation behaviour for MUPS play an important role in the development and health-seeking behaviour for MUPS in their children. Therefore, recurrent or persistent GP consultations for MUPS among children may be better conceptualised within a family context. Future research using a comprehensive model that incorporates both biological and psychosocial factors may shed light on what parental factors have the most influence on the development of MUPS and related GP consultations in their children.

Chapter 9. Prognosis of GP consultations for MUPS in children: a prospective cohort study

9.1. Introduction

This chapter is looking at prognosis following the child consultations for MUPS and whether previous exposure to maternal GP consultations for MUPS influences this. Prognosis within this chapter is concerned with persistence of GP consultations for MUPS in children. This chapter included a cohort of 1437 children who consulted for MUPS in primary care in 2009 and were prospectively followed up for one-year.

9.2. Aims and objectives

The primary aim of this chapter is to examine the association between exposure to maternal GP consultation for MUPS and persistence of GP consultation for MUPS in children.

The specific objectives include:

1. To quantify the frequency of persistent GP consultations for MUPS and identify the most common persistent MUPS in children.
2. To investigate the association between exposure to maternal GP consultation for MUPS and persistent GP consultation for MUPS in children. This includes investigating the following hypotheses, which are based on the results of the previous chapter (chapter 8):

(a) There is an association between maternal GP consultation for painful MUPS and persistence of GP consultation for painful MUPS in the child.

(b) There is no association between maternal GP consultation for not-painful MUPS and persistent GP consultation for not-painful MUPS in the child.

(c) There is an association between maternal GP consultation for gastrointestinal, musculoskeletal, and neurologic MUPS and persistent consultations for these MUPS in children. GP consultations for cardiopulmonary and urogenital MUPS were excluded from this analysis, because only small proportions of children have consulted for these MUPS based on the results of previous chapters.

3. To identify other predictors of persistent consultations for MUPS in children.

9.3. Methods

9.3.1. Study design and setting

To achieve the above stated aim and objectives, this chapter used a prospective cohort study design. This analysis was performed using GP consultation data from the twelve GP practices contributing to the CiPCA database (see section 5.2.1).

9.3.2. Study population

Eligible populations were children and their mothers registered with any of the 12 CiPCA GP practices between January 2007 and December 2010.

The cohort in this chapter consisted of all children who were aged 2 to 16 years and consulted a GP for MUPS in 2009.

9.3.3. Data collection

Data on exposure to maternal GP consultation for MUPS, outcome measures, and predictor variables were extracted from the CiPCA and the DiPCA databases.

9.3.3.1. Exposure to maternal consultation for MUPS

In this chapter, the child's exposure to maternal GP consultation for MUPS is the main predictor of interest for persistent GP consultation for MUPS in children. This is defined as the child's exposure to at least one maternal GP consultation for MUPS between 1 January 2007 and 31 December 2008. All included children were born before 1 January 2007.

The following measures of maternal GP consultation for MUPS were extracted from the mother's recorded GP consultations between 2007 and 2008:

- Maternal GP consultation status (yes, no) for MUPS.
- Maternal GP consultation status for painful and not-painful MUPS.

- Maternal GP consultation status for gastrointestinal, musculoskeletal and neurologic MUPS.

9.3.3.2. Outcome measures

As discussed in chapter 3 (section 3.7.1), prognosis refers to predicting the probability or risk of future outcomes (good or poor) in patients with a particular disease or health condition. In this chapter, the main outcome measure is persistence of GP consultations for MUPS in children, which will be used as an indicator for a poor outcome (poor prognosis). In this analysis, this is defined as persistence of GP consultations for MUPS in children in the year 2010 among those who consulted for MUPS in 2009. The reason for using this relatively short duration to measure persistent consultations for MUPS in children is because their consultation data for 2011 and 2012 were not available at the time of conducting this study. Also, using their consultation data before 2009 was not feasible as the temporal relationship between exposure to maternal consultation for MUPS and subsequent child consultation for MUPS needed to be maintained.

To measure this outcome, all children who consulted a GP for MUPS at least once in 2009 were identified and followed up during 2010. Recorded GP consultations for these children in 2010 were then used to categorise them into two groups based on their GP consultation status (yes, no) for MUPS in 2010:

- Persistent consulters for MUPS: this group included all children who consulted for MUPS in 2009 and 2010.

- Non-persistent consulters for MUPS: this group consisted of children who consulted for MUPS in 2009 but not in 2010.

The same method was used to measure other outcomes of interest, including persistence of GP consultation for painful and not-painful MUPS in this cohort of children.

9.3.4. Sociodemographic variables and potential effect modifiers

Predictor variables include child sex and age group, child birth order, household members count, IMD 2007 score, maternal age group, child GP consultation frequency, GP practice, and maternal history of anxiety or depressive disorders. Detailed description of all these variables and their measurements is presented under sections 7.3.6.2 and 7.3.6.3.

9.3.5. Statistical analysis

Descriptive statistics were used to describe the sociodemographic and health related characteristics of children and their mothers. Chi-squared tests and Mann-Whitney U tests were performed to test for significant baseline differences between exposed and unexposed children to maternal GP consultation for MUPS.

The Cox proportional hazards regression method was used to model the persistence of GP consultations for MUPS in children. The Cox proportional hazards regression can be used to model the time to (incidence or hazard) a particular event or outcome to occur according to values of the predictor variables under study (Kestenbaum, 2009f). In the context of this chapter, the Cox

proportional Hazards regression model was used to model the hazard rate of persistent GP consultations for MUPS in children in 2010 based on the child exposure status (yes, no) to maternal GP consultation for MUPS while controlling for other predictor. The Cox proportional Hazards model produces the hazard ratio (HR), which is a measure of the effect of a given predictor on the hazard of an individual to develop the outcome of interest during the follow up period (Liu, 2012).

The HR is interpreted in the same way as the relative risk (RR) (Kestenbaum, 2009f). Therefore, the RR (with 95% CI) was used to summarise the magnitude of association between exposure to maternal GP consultations for MUPS and persistent GP consultations for MUPS in children.

The Cox regression procedure in SPSS was used to analyse the data (IBM Corp, 2011). A time-constant variable was created in the data and entered in the "time function" box in the Cox regression procedure to indicate which children have persistent consultations for MUPS in 2010. In this variable, all children who have consulted for MUPS in 2010 were given a value of 1 indicating that they have developed the outcome, and a value of 2 was given to the remaining children to indicate that they were censored at a later time.

Univariable analyses were performed to examine the association between each predictor and the persistence of GP consultation for MUPS in children. All significant predictors of persistent GP consultations for MUPS with a *p*-value of <0.25 were included in the multivariable analysis. A justification for choosing this statistical criterion for variables selection is presented under section 7.3.7.

9.4. Results

9.4.1. Characteristics of children

1437 child-mother pairs were included. Differences in baseline characteristics of children exposed and unexposed to maternal GP consultation for MUPS are presented in table 9.1. There were no statistically significant differences between children exposed and unexposed to maternal GP consultation for MUPS in all baseline characteristics except for child birth order and maternal history of anxiety or depression disorders. Higher proportions of children exposed to maternal GP consultation for MUPS were “not first” in birth order (44%) than unexposed children (38%), *p* 0.029. Also, 37% of exposed and 13% of unexposed children had a history of maternal anxiety or depression disorders (*p* <0.000).

9.4.2. Proportions of children with persistent consultations for MUPS

Overall, 27% of all children had persistent consultations for MUPS in 2010. 25% and 15% of children had persistent consultations for painful and not-painful MUPS, respectively. 18% of all children had persistent consultations for back pain, 17% for constipation, and 15% for abdominal pain.

Table 9.1. Baseline sociodemographic characteristics of children

Variable	Exposed to maternal MUPS[c] consultation	Unexposed to maternal MUPS consultation	*p*-value
Child age[a,b]	9.5 (4.5)	9.5 (4.9)	0.744
Child age group 2009			
2-6 years	229 (32.6%)	254 (34.6%)	0.069
7-11 years	188 (26.7%)	158 (21.5%)	
12-16 years	286 (40.7%)	322 (43.9%)	
Gender			
Female	392 (55.8%)	398 (54.2%)	0.594
Male	311 (44.2%)	336 (45.8%)	
Mother age	37.8 (7.7)	37.5 (7.9)	0.465
Mother age group			
18-28	94 (13.4%)	113 (15.4%)	0.470
29-39	305 (43.4%)	301 (41.0%)	
40-50	269 (38.3%)	291 (39.6%)	
51-61	35 (5.0%)	29 (4.0%)	
Child birth order			
First	391 (55.6%)	451 (61.4%)	0.029
Not first	312 (44.4%)	283 (38.6%)	
Household members' count			
≤3	368 (52.3%)	411 (56.0%)	0.182
>3	335 (47.7%)	323 (44.0%)	
IMD 2007quintiles			
I	139 (19.9%)	167 (22.9%)	0.161
II	136 (19.5%)	144 (19.8%)	
III	143 (20.5%)	154 (21.1%)	
IV	166 (23.7%)	135 (18.5%)	
V	115 (16.5%)	129 (17.7%)	
Missing IMD score	4 (0.5%)	5 (0.7%)	
Maternal history of anxiety/depression			
Yes	262 (37.3%)	99 (13.5%)	<0.001
No	441 (62.7%)	635 (86.5%)	

[a]Data are means (SD) or numbers (%); [b]Percentages may not total 100 due to rounding; [c]Medically unexplained physical symptoms

9.4.3. The associations between exposure to maternal consultation for MUPS and persistence of similar consultations in children

The results showed that children exposed to maternal consultation for MUPS had significantly higher risk of having persistent consultations for MUPS than unexposed children (adjusted RR 1.29, 95% CI 1.05 to 1.58).

Children exposed to maternal consultation for painful MUPS also had increased risk of having persistent consultations for painful MUPS as compared to unexposed children (adjusted RR 1.32, 95% CI 1.02 to 1.71).

An association was found between exposure to maternal consultation for not-MUPS and persistence of consultations for not-painful MUPS, but this association was not statistically significant (adjusted RR 1.24, 95% CI 0.75 to 2.04).

Exposure to maternal consultation for gastrointestinal and neurologic MUPS was associated with increased risk of persistent consultations for gastrointestinal (adjusted RR 1.60, 95% CI 1.05 to 2.45) and neurologic MUPS in children (adjusted RR 2.28, 95% CI 1.03 to 5.05). However, a non-statistically significant association was found between exposure to maternal consultation for musculoskeletal MUPS and persistent consultation for similar MUPS in children (adjusted RR 1.32, 95% CI 0.84 to 2.08).

9.4.4. Other predictors of persistent consultation for MUPS in children

Table 9.2 presents the associations between all included predictors and persistence of GP consultations for MUPS in children, with crude and adjusted

RRs and 95% CIs. As shown in table 9.2, in addition to exposure to maternal GP consultation for MUPS, the child GP consultation frequency and age group were the only statistically significant predictors of persistent GP consultations for MUPS. Older children and frequent consulter children had increased risk of having persistent consultations for MUPS than other children, see table 9.2.

Table 9.2. Predictors of persistent GP consultation for MUPS in children

	Persistent consulters for MUPS[a] (n= 390)	Non-persistent consulters for MUPS (n= 1047)	Crude RR[b] (95% CIs[c])	Adjusted RR (95% CIs)
Child sex				
Male	163	484		
Female	227	563	1.14 (0.93, 1.40)	1.16 (0.95, 1.42)
Child age group				
2-6 years	90	393		
7-11 years	94	252	1.46 (1.09, 1.95)	1.42 (1.06, 1.90)
12-16 years	206	402	1.82 (1.42, 2.32)	1.77 (1.38, 2.27)
Child birth order				
Not first	160	435		
First	230	612	1.02 (0.83, 1.24)	1.10 (0.90, 1.35)
Household Members' count				
>3	183	475		
=<3	207	572	0.96 (0.78, 1.17)	0.99 (0.79, 1.24)
IMD 2007 quintiles				
1	75	231		
2	70	210	1.02 (0.74, 1.41)	1.02 (0.74, 1.42)
3	84	213	1.15 (0.85, 1.58)	1.11 (0.81, 1.52)
4	94	207	1.27 (0.94, 1.73)	1.22 (0.90, 1.65)
5	65	179	1.09 (0.78, 1.52)	1.12 (0.80, 1.56)
Maternal age group				
18-28 years	47	160		
29-39 years	148	458	1.08 (0.78, 1.49)	0.83 (0.59, 1.19)
40-50 years	170	390	1.34 (0.97, 1.85)	0.84 (0.57, 1.24)
51-61years	25	39	1.72 (1.06, 2.80)	1.07 (0.61, 1.85)
Maternal consultation status for MUPS				
No	166	568		
Yes	224	479	1.41 (1.15, 1.72)	1.29 (1.05, 1.58)

	Persistent consulters for MUPS[a] (n= 390)	Non-persistent consulters for MUPS (n= 1047)	Crude RR[b] (95% CIs[c])	Adjusted RR (95% CIs)
Maternal history of anxiety or depression				
No	276	800		
Yes	114	247	1.23 (0.99, 1.53)	1.12 (0.90, 1.41)
Child GP consultation frequency				
NFC[d]	306	1010		
FQ[e]	84	37	2.99 (2.35, 3.80)	2.80 (2.20, 3.58)

[a]Medically unexplained physical symptoms; [b]Relative risk; [c]Confidence intervals; [d]Non-frequent consulters; [e]Frequent consulters

9.5. Discussion

9.5.1. Summary of main findings

This chapter examined the persistence of GP consultations for MUPS in children, and investigated whether exposure to maternal GP consultations for MUPS influence it. More than one quarter of all children (27%) had persistent GP consultations for MUPS during the one-year follow up period. Back pain, constipation, and abdominal pain were the most common persistent MUPS in children.

As hypothesised, children exposed to maternal GP consultation for MUPS and painful MUPS had significantly higher risk of persistent consultations for MUPS and painful MUPS than unexposed children. Also, children exposed to maternal GP consultations for not-painful MUPS were at increased risk of having persistent consultations for not-painful MUPS, but this association was not statistically significant. Additionally, this analysis found associations between child exposure to

maternal GP consultations for gastrointestinal, neurologic, and musculoskeletal MUPS and increased risk of persistent consultations for these MUPS in children. However, these findings were only statistically significant for gastrointestinal and neurologic MUPS.

In addition to exposure to maternal consultations for MUPS, the child GP consultation frequency and older age group were they only statistically significant predictors of persistent GP consultations for MUPS in this cohort of children.

9.5.2. Comparison with existing literature

As far as the author is aware, this is the first study to examine the influence of exposure to maternal GP consultations for MUPS on persistence of GP consultations for MUPS in children. Despite the lack of similar studies to compare these findings with, prior research in this field provides indirect support to the findings of the current study. Levy and his colleagues (2000) reported that children of parents with IBS had more primary care consultations for gastrointestinal symptoms over a three-year period than children of parents without IBS diagnosis. In a case-control study, nested within a birth cohort study, MUPS among adults aged 36 years were significantly associated with abdominal pain and poor parental health when participants were aged 15 years (Hotopf et al., 1999). In the same cohort, headache in childhood was linked to headache (OR 2.22, 95% CI 1.62 to 3.06), multiple MUPS (OR 2.22, 95% CI 1.62 to 3.06), and psychiatric disorders in adulthood (OR 1.41, 95% CI 1.20 to 1.66) (Fearon & Hotopf, 2001).

The frequency of persistent consultations for MUPS observed in this cohort is similar to those reported in previous studies. A systematic review of 18 cohort

studies which examined the prognosis of recurrence/persistence of abdominal pain among children reported that 29% of children with abdominal pain at baseline had recurrent/persistent abdominal pain at various follow-up periods, ranging between 1-year and 5-year periods (Gieteling et al., 2008).

The finding of this study that older child age group is significantly associated with persistent consultations for MUPS also accords with the results of other population-based cohort studies, which reported older child age as a significant predictor of persistent MUPS in children (El-Metwally et al., 2004, Mikkelsson et al., 2008).

9.5.3. Interpretation

The current study has demonstrated that about three out every ten children had persistent consultations for MUPS over a one-year period. Despite the lack of long-term prognostic studies on children with MUPS in primary care, this finding suggests that considerable proportions of children may experience recurrent or persistent poor health during childhood, which might also extend to adulthood, based on the findings of previous studies (see sections 2.6.2 and 2.6.3).

The observed association between exposure to maternal GP consultations for MUPS and persistent GP consultations for MUPS is yet to be explained. However, as discussed before, both genetic and environmental factors may explain this. Also, persistent consultations for MUPS in children could be due to undiagnosed organic pathology or psychiatric disorders such as anxiety or depression. Previous studies in primary care (Campo et al., 2007) and secondary care (Walker &

Greene, 1989) found high levels of anxiety and depressive symptoms among children with RAP and their parents. Additionally, several population-based cohort studies of children have demonstrated that psychological stress and adverse social factors are significant predictors of recurrent or persistent MUPS (El-Metwally et al., 2004, Mikkelsson et al., 2008, Rimes et al., 2007, El-Metwally et al., 2007). These findings also agree with the results of primary care studies in adults. For example, a primary care study reported that psychological distress was significantly associated with persistent gastrointestinal physical symptom in adult patients (Halder et al., 2010).

9.5.4. Strengths and limitations

One of the main strengths of this study is that the data on GP consultations for MUPS in children was collected prospectively over a one-year period, thus it was able to estimate the relative risk of persistent GP consultations for MUPS due to exposure to maternal consultations for MUPS. Also, the child exposure to maternal GP consultations was measured using documented GP attendance which is a more precise measurement of exposures than measurements relying on recall. Another important strength is that the exposure to maternal GP consultation for MUPS was measured before persistent GP consultations for MUPS in children occur, which provide a clear temporal relationship. Additionally, all included mothers and children were registered with the CiPCA practices between 2007 and 2010, thus no losses to follow up, which increases the internal and external validity of the study.

This study also has some limitations which should be considered when interpreting its findings. This study was not able to assemble an inception cohort of children presenting for the first time with MUPS in primary care to ensure that they are comparable according to the time of the onset of their physical symptoms. As discussed under section 3.7.1, selecting an inception cohort of patients with poorly defined conditions such as MUPS based on the time of onset of symptoms is not feasible in primary care (Hay & Dunn, 2009). However, this cohort of children included a group of consecutive consulters for MUPS, which was clearly defined and assembled at the time of the child consultation for MUPS. Also, this cohort of children is likely to be generalised to all children presenting with MUPS in primary care because we would expect that both new and recurrent/persistent cases were included in this cohort.

Another limitation is that this study did not measure persistence of MUPS in children and only measured persistence of GP consultations for MUPS over one year period as a proxy for that. Also, the term “persistence” does not necessarily mean that children in 2010 had persistent consultations for the same type of MUPS they consulted with in 2009 (e.g. abdominal pain). Furthermore, as discussed under section 9.3.3.2, it was not possible to use a longer follow-up period to measure persistence of consultations for MUPS in children. Using longer follow-up period might improve precision, as there would be more outcome events measured. However, it is unlikely that using a longer period of follow-up would affect the associations found in this study. This is because there were enough recurrent/persistent consultations for MUPS among children to do the analysis.

In addition to potential for misclassification bias or errors in coding of MUPS, it is possible that some recurrent consultations for MUPS in children were requested by the GP (follow up consultations). However, this seems unlikely to completely explain the findings of this study. This is because it is not likely that GPs have initiated follow up consultations with children only based on the child's history exposure to maternal GP consultations for MUPS or older child age group. Also, if the GPs have requested follow up consultations for large proportions of children with MUPS, which we would expect to occur at random, then these significant associations would have disappeared.

Another limitation is that it was not feasible, based on consultation data, to measure and account for psychosocial factors in children which were reported as significant predictors of recurrence or persistence of MUPS in children (e.g. stress and adverse life events). However, it is unlikely for these factors to attenuate the observed association unless if they were associated with previous child's exposure to maternal consultation for MUPS.

9.5.5. Generalisability

As discussed above, this study assembled a clearly defined cohort of consecutive consulters for MUPS at the time of their GP consultation, and it was followed up over one-year. Also, exposure to maternal GP consultation for MUPS preceded the children consultation, and this was ascertained using documented GP consultation data. Also, this cohort of children consisted of all children from 12 GP practices, thus eliminated the chance of selection bias. This has enhanced the

internal and external validity of this study, and therefore these findings are highly likely to be generalisable to all children consulting in primary care.

9.5.6. Implications for clinical practice and future research

This study has provided important information on the likely prognosis of children consulting with MUPS in primary care. The results of this study suggest that these children deserve careful assessment, and provide a rationale for attempting to prevent MUPS in these children from becoming persistent and chronic. As discussed in chapter 7 (section 7.5.6), there is some evidence that CBT targeting children's coping responses to MUPS and parents' responses to pain in their children was associated with a significant reduction in severity of MUPS in children and a decrease in parental protective responses to pain in their children at 6-month follow-up (Levy et al., 2010). However, it is not fully clear as yet whether such interventions can also prevent the recurrence or persistence of GP consultations for MUPS in children. Therefore, further work is needed to identify and develop effective management strategies to prevent persistent consultations for MUPS in children. Also, more prospective research with longer follow up periods is needed to further examine the prognosis of children presenting with MUPS in primary care, and assess if persistent consultations during childhood also extend to adulthood. Additionally, more research is required to fully explain the exact mechanisms underlying the relationship between exposure to maternal consultation for MUPS and the persistence of similar consultations in the child.

9.6. Conclusion

This study showed that considerable proportions of children have persistent GP consultations for MUPS, which is influenced by previous exposure to maternal GP consultations for MUPS. These findings suggest that children and parents with recurrent or persistent GP consultations for MUPS should be targeted with appropriate interventions aiming at preventing MUPS from becoming chronic and reduce its negative impact on these families and healthcare resources. More research with longer follow-up periods is urgently needed to fully explain the influence of parental health on the health and consulting behaviour in the child.

Chapter 10. Discussion

This thesis has investigated the association between GP consultation for MUPS in parents and children. This thesis included five studies, the main findings of each are considered below.

10.1. Summary of main findings

This thesis has contributed to the knowledge base by showing that maternal GP consultation for MUPS is associated with similar consultations in the child, with persistent consultations for MUPS in children.

10.1.1. GP consultations for MUPS in parents and their children: a systematic review

The systematic review identified the lack of observational studies investigating the association of GP consultations for MUPS between parents and their children. The 8 included studies found only limited evidence of an association between GP consultations for MUPS in parents and children. Studies tended to focus on specific MUPS (e.g. abdominal pain, back pain) or symptoms group such as gastrointestinal MUPS in specific age groups, and typically relied on the self-report of MUPS and GP consultations.

10.1.2. The epidemiology of MUPS among children in Primary Care

This descriptive study has demonstrated that GP consultations for MUPS are common in children, with an annual GP consultation prevalence of 21%. This study also demonstrated that 12% of the overall number of GP consultations among children was for MUPS. Gastrointestinal, musculoskeletal, and neurological MUPS were the most common MUPS groups, whilst abdominal pain, vomiting, and headache were the most common presenting MUPS. Older children had more GP consultations for MUPS than younger children.

10.1.3. The association between GP consultations for MUPS between parents and children: a case-control study

This study showed that children consulting for MUPS were more likely to have mothers who had consulted for MUPS cases than children who did not consult for MUPS. No association was found between GP consultations for MUPS in fathers and children. However, children who had both parents consulting for MUPS were at increased odds of consulting for MUPS than children whose parents did not consult for MUPS. Additionally, dose-response relationships were found between numbers of consultations for MUPS and numbers of MUPS in mothers and their children.

10.1.4. The association between GP consultations for specific MUPS in mothers and children: a case-control study

The results of this study indicated that children consulting for painful and not-painful MUPS were more likely to have mothers who had consulted for painful and not-painful MUPS than children who did not consult for these MUPS. However, after adjustment for other variables, this association remained statistically significant only for painful MUPS. Also, dose-response relationships were found between numbers of consultations for painful MUPS and numbers of painful MUPS in the mother and the child.

This study has also found significant associations for GP consultations for musculoskeletal, gastrointestinal, and neurological MUPS in mothers and their children. Additionally, significant associations were observed between GP consultations for specific MUPS (mostly painful MUPS) in mothers and children, including abdominal pain, vomiting, joint pain, pain in extremities, and headache.

10.1.5. Prognosis of GP consultations for MUPS in children: a prospective cohort study

This study found that 27% of children who consulted for MUPS at baseline had persistent GP consultations for MUPS during a one-year follow up period. In this cohort of children, those who have been exposed to maternal GP consultation for MUPS and painful MUPS had higher risk of persistent consultations for MUPS and painful MUPS than unexposed children. Additionally, statistically significant associations were found between child exposure to maternal GP consultation for

gastrointestinal and neurologic MUPS and increased risk of persistent consultations for these MUPS in the child.

Other significant predictors of persistent GP consultations for MUPS in children were older child age group and frequent GP consultations for any reason.

10.2. Potential mechanisms for the association between GP consultations for MUPS in mothers and children

The exact mechanisms underlying the association between GP consultations for MUPS in mothers and children is not fully clear. However, existing literature suggests that this could be due to multiple factors including genetic and environmental factors. The findings of epidemiological studies in twins investigating the relative contribution of genetic and environmental factors to MUPS (including IBS, GI symptoms, LBP, headache) showed that both genetic and environmental (e.g. psychosocial) factors contribute to MUPS, but it seems that environmental factors have a greater influence (Levy et al., 2001, El-Metwally et al., 2008, Fowler et al., 2006, Mohammed et al., 2005). For example, a twin study by El-Metwally and colleagues (2008) found that only 41% of the total variance in LBP among 1790 children could be explained by genetic factors and 51% by environmental factors.

In the context of this thesis, one of the main limitations of such twin studies is that they relied on self-reported data on the occurrence of MUPS in the general population. Therefore, the contribution of the genetic and environmental factors could be different in parents and children consulting with MUPS. Although the role of genetic factors cannot be excluded as one of the main plausible explanations

for the association between consultations for MUPS in mothers and children, it seems that the influence of environmental factors in more important. This is because the association between consultations for MUPS in parents and children was only statistically significant for mother-child pairs, and we would expect a significant association for father-child pairs if genetic factors had a major contribution.

One important environmental factor which has been hypothesised to explain the association between GP consultations for MUPS in parents and children is childhood social learning of illness and healthcare seeking behaviour (Craig et al., 2002, Levy et al., 2007, Cardol et al., 2007, Levy et al., 2000). A number of studies showed that parental responses and attitudes toward the child illness (reinforcement) and parental coping mechanisms with their own illness (role modelling) may influence symptoms frequency, disability days, and healthcare consultations in their children (Whitehead et al., 1994, Walker & Zeman, 1992). For example, in the study by Whitehead and colleagues (1994), women with IBS were more likely than women without IBS to emulate the illness behaviour of their parents and to recall that their parents reinforced illness behaviour by rewarding them with special privileges, such as excluding them from household duties, special attention, or treat foods in their childhood. The findings of this thesis agree with the childhood social learning of illness behaviour hypothesis by showing an association between GP consultations for MUPS in mothers (not fathers) and children. However, we would expect social learning and role modelling to increase with child's age, but the result of this thesis showed no significant interaction effects between the child age group (or other independent variables) and maternal consultations for MUPS on the child GP consultation status for MUPS. This

suggests that the maternal effect on child consultations for MUPS through "reinforcement" is present at all ages and represent a more important influence.

The above stated findings and statements raise questions about why, how, and when maternal illness behaviour is transmitted to the child. Unfortunately, the current literature has no empirically tested models that address these questions. However, mothers are traditionally responsible for raising children and usually spend more time with them. Therefore, the mother might be the first person to notice or perceive symptoms in her child and then decide whether to seek healthcare for the child or not, which can be influence by the mother's definition of health and illness and attitudes towards healthcare (Campbell & Roland, 1996). Thus, the mother models for her child how to interpret and perceive symptoms of ill health and when to seek healthcare (Moran & O'Hara, 2006). These statements provide a plausible explanation for the findings of this thesis and agree with previous studies which found maternal healthcare use a significant predictor of child's health seeking behaviour (Ward & Pratt, 1996, Schor et al., 1987). For example, one study found that maternal influence on primary care consultations in children is two to three times greater than paternal influence (Schor et al., 1987).

In this thesis, the association between GP consultations for MUPS in mothers and children was clearest for painful MUPS. Also, maternal consultation for painful MUPS was associated with persistent consultations for painful MUPS in children. This suggest that maternal influence on the child's social learning of illness behaviour through "reinforcement" is more influential and lasting for painful than not-painful conditions. It is well established that pain sensation has emotional components and affective changes such as anxiety and depression, and thus pain

can be subject to psychosocial influences or responses from family members (Bebbington & Delemos, 1996). Also, prior studies have shown that parental consultation for painful MUPS in their children is influenced by level of pain severity, functional disability, and perceived seriousness of the symptoms (Perquin et al., 2000b, Perquin et al., 2001, Boey & Goh, 2001a, Masiero et al., 2010). So, probably parents perceive painful MUPS in themselves and in their children as more serious than not-painful MUPS, which influence their GP consultation rates for MUPS. Additionally, protective parental responses to pain in their children were found to play an important role in pain catastrophising in adolescents with chronic musculoskeletal pain (Guite et al., 2011). Also, families presenting in primary care for abdominal pain in their children had greater worries and beliefs scores about abdominal pain than other families who did not consult for their children with abdominal pain (van Tilburg et al., 2009).

10.3. Strengths and limitations

One of the key strengths of this thesis is its large sample size and comprehensiveness assessment of MUPS in parents and children. This thesis included all available children, covering all age groups (0 to 16 years), and their parents registered with 12 research GP practices. The numbers of included children and parents easily provided the numbers required based on sample size calculations. The advantages for this is less sampling variation, reduced chance of selection bias, and more precision in detecting and quantifying the association between GP consultations for MUPS in parents and child. In this thesis, only one

child per household was included in order to facilitate the analysis of data and interpretation of findings. However, this is unlikely to have affected the internal validity of the findings because included children were randomly selected. Also, all the GP practices contributing to the CiPCA database were included. This has increased the external validity of the findings of this thesis by avoiding the potential for biases which may arise due to differences in characteristics of registered populations, number of GPs in each practice, and GP behaviour.

Another strength of this thesis is that it has included children from all age groups and used a broad list of MUPS, which allowed a comprehensive examination of the whole spectrum of MUPS experienced by parents and children across age groups. Studies focusing on specific symptoms in certain age groups are important but they fail to identify children at risk of developing other MUPS across different age groups. Also studies including specific MUPS do not provide information about the association between MUPS in parents and children presenting with other MUPS. This thesis provided information on the association between GP consultations for a broad list of MUPS in parents and children, and therefore these findings are generalisable to all children presenting with MUPS in primary care.

According to the Department of Health (2011), over 97% of the UK population is registered with GP practices, and the GP is the first point of access to non-emergency healthcare in the UK. Therefore, it is unlikely that many children or parents consulting for MUPS were missed. The CiPCA GP practices included in this thesis are volunteer research network practices and the characteristics of their registered populations may differ from the other practices registered populations.

However, one study of 66 research network GP practices and 749 other GP practices in a nearby region found no significant differences between those practices in characteristics of their registered patients (Hammersley et al., 2002). Therefore, these findings of this thesis are likely to be generalisable to other GP practices in the UK.

Another strength is that these findings are based on documented GP attendance which is a more precise source of information about consultations for MUPS than self-reported data which is prone to recall bias. However, GP consultation data has some limitations which are considered below.

One of the limitations of this thesis is that family members were identified based on full address details and surnames for practice registered populations. It is possible that some errors may have occurred in identifying the parents of included children. However, it is unlikely that such errors have occurred for large proportions of children, because family members usually register with the same GP practice (Simon, 2008). Additionally, the household structure for the CiPCA households for selected children were almost identical to the structure of households with children in the UK based on data from the Office for National Statistics on live births by age group of mother and father at birth of the baby, percentages of number of children in the family, and age group of the youngest child in the household. Another limitation is that 41% of fathers of included children were not identified, because fathers were registered with other practices or were not registered with any practice, or because children were living with single-mothers. So, exposure status for paternal GP consultations for MUPS for a considerable proportion of children was unknown. However, this is unlikely to have

affected the internal validity of the findings, because the proportions of children with missing paternal data were evenly distributed between consulters and non-consulters for MUPS. Also the numbers of children with paternal consultation data were more than those needed based on sample size calculations. Therefore, the non- statistically significant association between GP consultations for MUPS in fathers and children found in this thesis is unlikely to be explained by low statistical power.

Children consulting for MUPS were identified using a comprehensive list of standardised diagnostic Read codes which are routinely used in primary care in the UK. It is possible that a minority of children presenting with MUPS may have been missed. However, a practicing GP (CM) was involved in selection of the list of Read codes which may minimise the possibility of missing codes.

Another limitation of using diagnostic codes is that they may not identify all patients consulting for MUPS, because of coding misclassification, incompleteness of records, or poor diagnostic skills. However, the CiPCA database has been shown to be a high quality dataset (Porcheret et al., 2004), and data from CiPCA were comparable to data from larger national general practice databases (Jordan et al., 2007). Also, documented patient attendance at general practice is more likely to be complete as it is a legal requirement for all GP practices in the UK. In 2006, 97% of all GP consultations that occurred at the CiPCA GP practices were given a morbidity Read code (Jordan et al., 2010). Additionally, the current classification system used in primary care allows for coding definitive diagnoses as well as symptoms, which reduces the potential for diagnostic misclassification. Therefore, diagnostic misclassification or level of completeness of medical records

is not likely to have affected the validity of findings of this thesis. It is also possible that children consulting with MUPS may have been assigned other diagnostic codes, if they have presented with more than one complaint. However, this should not change the conclusions of this thesis unless this sort of misclassification was not occurring at random and was based on the child's history of previous exposure to parental GP consultation for MUPS, which is very unlikely.

Another type of bias which affects the internal validity of a study occurs if the identification of cases and controls is influenced by their exposure status. To avoid this type of bias, ascertainment of consultations status for MUPS in children and parents was carried out separately before merging their GP consultation data. Also, to ensure that ascertainment of cases and controls and their exposure to parental consultations for MUPS as objective as possible, the free-text records of their recorded consultations for MUPS were reviewed to judge whether MUPS were non-specific.

In this thesis, two main methods were used to control for potential confounding factors, matching and multivariable analyses. The most important potential confounding factors were measured and accounted for, including age, sex, parental age, area level deprivation, household member's count, birth order of the child, the child GP consultation frequency, parental history of anxiety and depressive disorders. However, it was not feasible, based on consultation data, to measure and account for some potential confounding factors, such as ethnicity and psychosocial factors (e.g. adverse life events). However, ethnicity was not found to be a significant predictor of GP consultations for MUPS in other studies of parents and children (Little et al., 2001, Boey & Goh, 2001c, Boey & Goh, 2001a).

Also, the crude odds ratios and relative risks did not change substantially after adjustment for the above mentioned potential confounding factors.

Many of the results of this thesis are in agreement with several previous studies in this field, including genetic studies. Also, the prospective cohort in this thesis has provided a clear temporal relationship between children exposure to maternal GP consultation for MUPS and subsequent persistent consultations for MUPS in the child. Additionally, the findings of this thesis were strengthened by evidence of dose-response relationships between number of GP consultations and number of MUPS in mothers and children.

Overall, considering all aspects related to the internal and external validity of this thesis, the results are likely to be generalisable to the UK primary care setting.

10.4. Implications for clinical practice and research

The findings of this thesis have important implications for general practice. The findings have demonstrated that maternal GP consultation for MUPS is associated with similar consultations in the child and information is given about specific MUPS in which this association becomes more apparent. Additionally, this thesis has provided information on the likely prognosis of children consulting with MUPS in primary care in relation to related previous exposure to maternal GP consultation for MUPS, and identified other predictors of persistent consultations for MUPS in children.

It is important that GPs be aware of this link. GPs may wish to screen families of children with recurrent or persistent consultations for MUPS. Recognising similarity

in consultation patterns for MUPS within families, especially frequent attending families, provide a rationale for the GPs respond differently, “not to wait and see”, and attempt to modify any inappropriate illness and consulting behaviour clustering within such families.

The findings of a systematic review of randomised controlled trials suggest that interventions such as family-focused CBT and self-management techniques are efficient in pain reduction and functional improvement among children with MUPS, such as abdominal pain and headache (Eccleston et al., 2002). A recent randomised controlled study has demonstrated that CBT targeting children’s coping responses to recurrent abdominal pain and parents’ responses to pain in their children was associated with significant reduction in pain and other GI symptoms severity (Levy et al., 2010). Also, parents of children in the CBT group reported greater decreases in their protective responses to pain in their children as compared to parents of children in the comparison group at the same points of follow-up. Another randomised controlled trial showed that CBT for children presenting in primary care and speciality clinics with persistent MUPS and anxiety was associated with significant improvements in anxiety symptoms and reduction in pain severity and discomfort due to GI MUPS (Warner et al., 2011). These findings appear to be promising in the management of children with MUPS. However, most of these trials were conducted in secondary care settings with relatively short term follow-up assessment (3 to 6 months). Additionally, these trials did not measure children’s consultations patterns for MUPS before and after CBT. So, it is not clear whether CBT had an impact on the consultation rate for MUPS in children. But, there is some research evidence that CBT and pharmacological therapy for adult patients presenting with MUPS in primary care

and general outpatient clinics are effective in reducing frequency of symptoms, the number of consultations, and psychological distress (Husain et al., 2007, Sumathipala et al., 2000, Speckens et al., 1995). Also, a randomised controlled trial in the UK showed that aerobic exercise training for primary care adult patients presenting with MUPS is effective in reducing number of consultations and prescriptions (Peters et al., 2002). Potentially, such interventions could impact on the illness and healthcare seeking behaviour of both parents and their children, but no studies exist to confirm or refute this.

These interventions could be implemented in primary care by offering parents of children with recurrent or persistent MUPS referral to CBT therapists in the community or secondary care settings. Also, emerging research evidence suggests that patients with recurrent MUPS can be managed in primary care by GPs with special interest in MUPS management. For example, in the UK, a pilot randomised controlled trial in primary care showed that managing patients presenting with MUPS in primary care-based “MUPS clinics” by GPs with special interest in MUPS is feasible and acceptable to patients (Burton et al., 2012). In this trial, the intervention included CBT aimed at modifying symptoms and their impact over four appointments (1 hour appointment and three 20 minute appointments).

The findings of this thesis also have implications for future research. Further prospective quantitative and qualitative research with longer follow up periods is needed to fully explain the exact parental and environmental factors that contribute to development of MUPS and related consulting behaviour among children. Qualitative research might uncover some of the complexities surrounding illness and consulting behaviour and get the views of parents and children themselves.

Such research should also use comprehensive models that incorporate both genetic and psychosocial factors and healthcare services use. Moreover, prognostic research with long follow up periods is required to further examine the prognosis of children presenting with MUPS in primary care, and assess if persistent consultations during childhood also extend to adulthood. Such research can provide valuable information about the aetiology of psychosomatic syndromes, somatisation disorder, and other psychiatric disorders.

Future research investigating the association between GP consultations for MUPS should measure other medical comorbidities in children and parents and investigate if the association between GP consultations for MUPS in parents and children just reflect patterns of GP consultations more generally.

Future randomised controlled trials testing interventions to improve health outcomes among children with MUPS should encompass family factors and involve parents in such interventions. Such research should also measure healthcare use for MUPS as a primary outcome variable.

In summary, this thesis has demonstrated that GP consultations for MUPS among children are very common, persist in considerable proportions of children, and influenced by previous exposure to maternal GP consultation for MUPS. The implications for primary care and future research are highlighted.

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Appendix 1. Detailed search strategy for the systematic review

MEDLINE database

Search #	Search term
1	FAMILY/
2	PARENTS/
3	mother$.ti,ab
4	father$.ti,ab
5	maternal.ti,ab
6	paternal.ti,ab
7	parent$.ti,ab
8	family.ti,ab
9	families.ti,ab
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	CHILD/
12	ADOLESCENT/
13	child$.ti,ab
14	teen$.ti,ab
15	adolescen$.ti,ab
16	Juvenile$.ti,ab
17	siblings.ti,ab
18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19	10 AND 18
20	CHILD OF IMPAIRED PARENTS/
21	PARENT-CHILD RELATION/
22	FAMILY HEALTH/
23	20 OR 21 OR 22
24	19 OR 23
25	PRIMARY HEALTH CARE/
26	COMMUNITY HEALTH SERVICES/
27	CHILD HEALTH SERVICES/
28	FAMILY PRACTICE/
29	PHYSICIANS, FAMILY/
30	PHYSICIAN'S PRACTICE PATTERNS/
31	(primary ADJ care).ti,ab
32	(primary ADJ health ADJ care).ti,ab
33	(general ADJ practice).ti,ab
34	(family ADJ practice).ti,ab
35	(family ADJ physician).ti,ab
36	(family ADJ doctor).ti,ab
37	AMBULATORY CARE/
38	25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39	REFERRAL AND CONSULTATION/
40	consult$.ti,ab
41	Visit$.ti,ab
42	attendance.ti,ab
43	attenders.ti,ab
44	presentation.ti,ab
45	(health ADJ care ADJ utilisation).ti,ab
46	(health ADJ care ADJ utilization).ti,ab
47	(health ADJ care ADJ seeking).ti,ab
48	(care ADJ seeking).ti,ab
49	(care AND seeking).ti,ab
50	39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49
51	38 AND 50
52	MUSCULOSKELETAL-DISEASES/
53	PAIN/
54	52 AND 53
55	HEADACHE/
56	TENSION-TYPE HEADACHE/
57	NECK PAIN/
58	SHOULDER PAIN/
59	BACK PAIN/
60	LOW BACK PAIN/
61	ABDOMINAL PAIN/
62	NEURALGIA/
63	ARTHRALGIA/
64	SOMATOFORM DISORDERS/
65	FIBROMYALGIA/
66	IRRITABLE BOWEL SYNDROME/
67	FATIGUE SYNDROME, CHRONIC/
68	(musculo$ ADJ pain).ti,ab
69	(muscular ADJ pain).ti,ab
70	(skeletal ADJ pain).ti,ab
71	(spine ADJ pain).ti,ab
72	(spinal ADJ pain).ti,ab
73	(back ADJ pain).ti,ab
74	(low AND back ADJ pain).ti,ab
75	(neck ADJ pain).ti,ab
76	(cervical ADJ pain).ti,ab
77	(knee$ ADJ pain).ti,ab
78	(hip ADJ pain).ti,ab
79	(shoulder$ ADJ pain).ti,ab
80	(flank ADJ pain).ti,ab
81	(buttock ADJ pain).ti,ab
82	myalgia.ti,ab
83	(joint$ ADJ pain).ti,ab
84	headache.ti,ab
85	ache.ti,ab
86	(abdominal ADJ pain).ti,ab
87	somatization.ti,ab
88	somatisation.ti,ab
89	(medically AND unexplained AND symptoms).ti,ab
90	(medically AND unexplained AND physical AND symptoms).ti,ab
91	(unexplained AND physical AND symptoms).ti,ab

92	(non-specific AND physical AND symptoms).ti,ab
93	(nonspecific AND physical AND symptoms).ti,ab
94	(non AND specific AND physical AND symptoms).ti,ab
95	54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94
96	EPIDEMIOLOGIC STUDIES/
97	CROSS-SECTIONAL STUDIES/
98	CASE-CONTROL STUDIES/
99	COHORT STUDIES/
100	PROSPECTIVE STUDIES/
101	RETROSPECTIVE STUDIES/
102	LONGITUDINAL STUDIES/
103	FOLLOW-UP STUDIES/
104	survey.ti,ab
105	96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104
106	24 AND 51 AND 95 AND 105
107	24 AND 51 AND 105
108	24 AND 95 AND 105

EMBASE database

Search #	Search term
1	FAMILY/
2	PARENT/
3	mother$.ti,ab
4	father$.ti,ab
5	maternal.ti,ab
6	paternal.ti,ab
7	parent$.ti,ab
8	family.ti,ab
9	families.ti,ab
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	CHILD/
12	ADOLESCENT/
13	child$.ti,ab
14	teen$.ti,ab
15	adolescen$.ti,ab
16	juvenile$.ti,ab
17	siblings.ti,ab
18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19	10 AND 18
20	CHILD PARENT RELATION/
21	FAMILY HEALTH/
22	19 OR 20 OR 21
23	PRIMARY HEALTH CARE/
24	COMMUNITY CARE/
25	CHILD HEALTH CARE/
26	FAMILY PRACTICE/
27	GENERAL PRACTITIONER/
28	GENERAL PRACTICE/
29	CLINICAL PRACTICE/
30	(primary ADJ care).ti,ab
31	(primary ADJ health ADJ care).ti,ab
32	(general ADJ practice).ti,ab
33	(family ADJ practice).ti,ab
34	(family ADJ physician).ti,ab
35	(family ADJ doctor).ti,ab
36	AMBULATORY CARE/
37	23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36
38	CONSULTATION/
39	PATIENT REFERRAL/
40	consult$.ti,ab
41	visit$.ti,ab
42	attendance.ti,ab
43	attenders.ti,ab
44	presentation.ti,ab
45	(health ADJ care ADJ utilization).ti,ab
46	(health ADJ care ADJ utilisation).ti,ab
47	(health ADJ care ADJ seeking).ti,ab
48	(care ADJ seeking).ti,ab
49	(care AND seeking).ti,ab
50	38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49
51	37 AND 50
52	MUSCULOSKELETAL DISEASE/
53	PAIN/
54	52 AND 53
55	HEADACHE/
56	TENSION HEADACHE/
57	NECK PAIN/
58	SHOULDER PAIN/
59	BACK PAIN/
60	LOW BACK PAIN/
61	ABDOMINAL PAIN/
62	ARTHRALGIA/
63	NEURALGIA/
64	SOMATOFORM DISORDER/
65	FIBROMYALGIA/
66	IRRITABLE COLON/
67	CHRONIC FATIGUE

	SYNDROME/
68	(musculo$ ADJ pain).ti,ab
69	(muscular ADJ pain).ti,ab
70	(skeletal ADJ pain).ti,ab
71	(spine ADJ pain).ti,ab
72	(spinal ADJ pain).ti,ab
73	(back ADJ pain).ti,ab
74	(low ADJ back ADJ pain).ti,ab
75	(neck ADJ pain).ti,ab
76	(cervical ADJ pain).ti,ab
77	(knee$ ADJ pain).ti,ab
78	(hip ADJ pain).ti,ab
79	(shoulder$ ADJ pain).ti,ab
80	(flank ADJ pain).ti,ab
81	(buttock ADJ pain).ti,ab
82	myalgia.ti,ab
83	(joint$ ADJ pain).ti,ab
84	headache.ti,ab
85	ache.ti,ab
86	(abdominal ADJ pain).ti,ab
87	somatization.ti,ab
88	somatisation.ti,ab
89	(medically AND unexplained AND symptoms).ti,ab
90	(medically AND unexplained AND physical AND symptoms).ti,ab
91	(unexplained AND physical AND symptoms).ti,ab
92	(non-specific AND physical AND symptoms).ti,ab
93	(nonspecific AND physical AND symptoms).ti,ab
94	(non AND specific AND physical AND symptoms).ti,ab
95	54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94
96	EPIDEMIOLOGY/
97	CROSS-SECTIONAL STUDY/
98	CASE-CONTROL STUDY/
99	COHORT ANALYSIS/
100	FOLLOW UP/
101	LONGITUDINAL STUDY/
102	RETROSPECTIVE STUDY/
103	PROSPECTIVE STUDY/
104	survey.ti,ab
105	96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104
106	22 AND 51 AND 95 AND 105
107	22 AND 51 AND 105
108	22 AND 95 AND 105

CINAHL database

Search #	Search term
1	FAMILY/
2	PARENTS/
3	mother$.ti,ab
4	father$.ti,ab
5	maternal.ti,ab
6	paternal.ti,ab
7	parent$.ti,ab
8	family.ti,ab
9	families.ti,ab
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	CHILD/
12	ADOLESCENCE/
13	child$.ti,ab
14	teen$.ti,ab
15	adolescence.ti,ab
16	adolescent$.ti,ab
17	juvenile$.ti,ab
18	siblings.ti,ab
19	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20	10 AND 19
21	CHILDREN OF IMPAIRED PARENTS/
22	PARENT-CHILD RELATIONS/
23	FAMILY HEALTH/
24	21 OR 22 OR 23
25	20 OR 24
26	COMMUNITY HEALTH SERVICES/
27	CHILD HEALTH SERVICES/
28	PRIMARY HEALTH CARE/
29	FAMILY PRACTICE/
30	PHYSICIANS, FAMILY/
31	PRACTICE PATTERNS/
32	(primary ADJ care).ti,ab
33	(primary ADJ health ADJ care).ti,ab
34	(general ADJ practice).ti,ab
35	(family ADJ practice).ti,ab
36	(family ADJ physician).ti,ab
37	(family ADJ doctor).ti,ab
38	AMBULATORY CARE/
39	26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38
40	REFERRAL AND CONSULTATION/
41	consult$.ti,ab
42	visit$.ti,ab
43	attendance.ti,ab
44	attenders.ti,ab
45	presentation.ti,ab

46	(health ADJ care ADJ utilization).ti,ab
47	(health ADJ care ADJ utilisation).ti,ab
48	(health ADJ care ADJ seeking).ti,ab
49	(care ADJ seeking).ti,ab
50	(care AND seeking).ti,ab
51	40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50
52	39 AND 51
53	MUSCULOSKELETAL DISEASES/
54	PAIN/
55	53 AND 54
56	HEADACHE/
57	TENSION HEADACHE/
58	NECK PAIN/
59	SHOULDER PAIN/
60	BACK PAIN/
61	LOW BACK PAIN/
62	ABDOMINAL PAIN/
63	ARTHRALGIA/
64	NEURALGIA/
65	SOMATOFORM DISORDERS/
66	FIBROMYALGIA/
67	FATIGUE SYNDROME, CHRONIC/
68	IRRITABLE BOWEL SYNDROME/
69	(musculo$ ADJ pain).ti,ab
70	(muscular ADJ pain).ti,ab
71	(skeletal ADJ pain).ti,ab
72	(spine ADJ pain).ti,ab
73	(spinal ADJ pain).ti,ab
74	(back ADJ pain).ti,ab
75	(low ADJ back ADJ pain).ti,ab
76	(neck ADJ pain).ti,ab
77	(cervical ADJ pain).ti,ab
78	(knee$ ADJ pain).ti,ab
79	(hip ADJ pain).ti,ab
80	(shoulder$ ADJ pain).ti,ab
81	(flank ADJ pain).ti,ab
82	(buttock ADJ pain).ti,ab
83	myalgia.ti,ab
84	(joint$ ADJ pain).ti,ab
85	headache.ti,ab
86	ache.ti,ab
87	(abdominal ADJ pain).ti,ab
88	somatization.ti,ab
89	somatisation.ti,ab
90	(medically AND unexplained AND symptoms).ti,ab
91	(medically AND unexplained AND physical AND symptoms).ti,ab
92	(unexplained AND physical AND symptoms).ti,ab
93	(non-specific AND physical AND symptoms).ti,ab
94	(nonspecific AND physical AND symptoms).ti,ab
95	(non AND specific AND physical AND symptoms).ti,ab
96	55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95
97	EPIDEMIOLOGICAL RESEARCH/
98	CROSS SECTIONAL STUDIES/
99	CASE CONTROL STUDIES/
100	RETROSPECTIVE PANEL STUDIES/
101	PROSPECTIVE STUDIES/
102	CONCURRENT PROSPECTIVE STUDIES/
103	survey.ti,ab
104	97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103
105	25 AND 52 AND 96 AND 104
106	25 AND 52 AND 104
107	25 AND 96 AND 104

PsycINFO database

Search #	**Search term**
1	FAMILY/
2	PARENTS/
3	mother$.ti,ab
4	father$.ti,ab
5	maternal.ti,ab
6	paternal.ti,ab
7	parent$.ti,ab
8	family.ti,ab
9	families.ti,ab
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	CHILD PSYCHOLOGY/
12	ADOLESCENT PSYCHOLOGY/
13	child$.ti,ab
14	teen$.ti,ab
15	adolescen$.ti,ab
16	juvenile$.ti,ab
17	siblings.ti,ab
18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19	10 AND 18

20	FATHER CHILD RELATIONS/
21	MOTHER CHILD RELATIONS/
22	PARENT CHILD RELATIONS/
23	HEALTH/
24	CAREGIVERS/
25	20 OR 21 OR 22 OR 23 OR 24
26	19 OR 25
27	PRIMARY HEALTH CARE/
28	HEALTH CARE SERVICES/
29	FAMILY PHYSICIANS/
30	GENERAL PRACTITIONERS/
31	FAMILY PHYSICIANS/
32	(primary ADJ care).ti,ab
33	(primary ADJ health ADJ care).ti,ab
34	(general ADJ practice).ti,ab
35	(family ADJ practice).ti,ab
36	(family ADJ physician).ti,ab
37	(family ADJ doctor).ti,ab
38	27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39	HEALTH CARE UTILIZATION/
40	PROFESSIONAL REFERRAL/
41	SELF REFERRAL/
42	PROFESSIONAL CONSULTATION/
43	consult$.ti,ab
44	visit$.ti,ab
45	attendance.ti,ab
46	attenders.ti,ab
47	presentation.ti,ab
48	(health ADJ care ADJ utilization).ti,ab
49	(health ADJ care ADJ utilisation).ti,ab
50	(health ADJ care ADJ seeking).ti,ab
51	(care ADJ seeking).ti,ab
52	(care AND seeking).ti,ab
53	39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52
54	38 AND 53
55	MUSCULOSKELETAL DISORDERS/
56	PAIN/
57	55 AND 56
58	HEADACHE/
59	NEURALGIA/
60	JOINT DISORDERS/
61	BACK PAIN/
62	SOMATOFORM DISORDERS/
63	FIBROMYALGIA/
64	IRRITABLE BOWEL SYNDROME/
65	CHRONIC FATIGUE SYNDROME/
66	(musculo$ ADJ pain).ti,ab
67	(muscular ADJ pain).ti,ab
68	(skeletal ADJ pain).ti,ab
69	(spine ADJ pain).ti,ab
70	(spinal ADJ pain).ti,ab
71	(back ADJ pain).ti,ab
72	(low AND back ADJ pain).ti,ab
73	(neck ADJ pain).ti,ab
74	(cervical ADJ pain).ti,ab
75	(knee$ ADJ pain).ti,ab
76	(hip ADJ pain).ti,ab
77	(shoulder$ ADJ pain).ti,ab
78	(flank ADJ pain).ti,ab
79	(buttock ADJ pain).ti,ab
80	myalgia.ti,ab
81	(joint$ ADJ pain).ti,ab
82	headache.ti,ab
83	ache.ti,ab
84	(abdominal ADJ pain).ti,ab
85	somatization.ti,ab
86	somatisation.ti,ab
87	(medically AND unexplained AND symptoms).ti,ab
88	(medically AND unexplained AND physical AND symptoms).ti,ab
89	(unexplained AND physical AND symptoms).ti,ab
90	(non-specific AND physical AND symptoms).ti,ab
91	(nonspecific AND physical AND symptoms).ti,ab
92	(non AND specific AND physical AND symptoms).ti,ab
93	57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92
94	EPIDEMIOLOGY/
95	RISK FACTORS/
96	FOLLOWUP STUDIES/
97	LONGITUDINAL STUDIES/
98	RETROSPECTIVE STUDIES/
99	PROSPECTIVE STUDIES/
100	survey.ti,ab
101	94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100
102	26 AND 54 AND 93 AND 101
103	26 AND 54 AND 101
104	26 AND 93 AND 101

Appendix 2. Data available within CiPCA and DiPCA databases

Consultations In Primary Care Archive (CIPCA)			
Field Name	**Type**	**Explanation**	**Example s**
Practice ID	Text	Unique letter code ascribed to GP Network practices	A, B, C etc
Sex	Text	Male, Female, Intermediate	M, F, I
Date of Birth	Date	Patient's date of birth	DD/MM/YY
Age	Numeric	Age in years on date of consultation.	
Consultation Date	Date	Date of consultation	DD/MM/YY
Location	Text	Place of consultation. See Network staff for detailed explanation of location. Descriptions of similar activity vary from practice to practice, and this variable has therefore been aggregated to “location group” (see below).	Urgent surgery, routine surgery, telephone, out of hours, etc
Location Group	Text	GP System-generated description for location of consultation.	Surgery, Home,Telephone
Read 4 Code	Text	4 digit alpha numeric code of diagnosis, symptom or process of medicine used by clinician to label the consultation - used in GPRN practice B only during 1998 - 2002.	
Read 4 Term	Text	The clinical term for the code. Practice B only during 1998 - 2002.	
Read 5 Code	Text	5 digit alpha numeric medical code. NB Read 5 is a totally different medical dictionary to Read 4 (consult Network staff for advice).	
Read 5 Term	Text	The clinical term for a Read 5 code.	
Episode	Text	A description of the status of the illness event.	First, New/Review, other
Staff Group	Text	Indicates which type of health professional the consultation was with.	GP Principal,GP Locum, Practice Nurse
GP ID	Text	Unique ID which can be linked to the name of the person the consultation was with (to be used when “who” field is stripped from the database as part of our anonymity database). Key is held by Network staff.	1, 2, 3
Unique ID	Text	Unique ID for each patient	A1234
Cons Text 2	Text	Free text entered at consultation. Provides additional or supplementary data to the read code and term. Limited numbers of characters are downloadable.	
Surgery*	Numeric	Coded 1 if consultation is face to face, by phone or home visit ; 0 otherwise	1 - data
Coded*	Numeric	Coded 1 if a Read Code recorded for consultation ; 0 otherwise	1 - data
Chapter*	Text	Read Code Chapter based on Read Code or local code	A, B, C
Read Code*	Text	The Read 5 Code with dashes and dots and all following characters removed. Aids searching for specific Read Codes	

Demographic Deprivation Data in Primary Care Archive (DIPCA)			
Field Name	Type	Explanation	Examples
PRACTICE CODE	Text	Unique letter code ascribed to GP Network practices	B
UNIQUE ID		Unique ID for each patient	B1234
DOB	Date	year dd/mm/yyyy	20/04/2004
SEX	Text	Male or female	M or F
POSTCODE	Text	Postcode of patient	ST5 5BG
DATE of deregistration or DEATH	Date	DD MM YYYY - date of de - registration or death (where available)	DD MM YYYY
# Denominator population data is available for two time points per year 31 July and 31st December per year			

Appendix 3. Read codes chapters

Chapter	Chapter name
Processes of care	
0….	Occupations
1….	History/symptoms
2….	Examinations? signs
3….	Diagnostic procedures
4….	Laboratory procedures
5….	Radiology/ physics in medicine
6….	Preventative procedures
7….	Operations, procedures, sites
8….	Other therapeutic procedures
9….	Administration
Diagnosis	
A....	Infectious/parasitic diseases
B....	Neoplasms
C....	Endocrine, nutrition and metabolic diseases
D....	Blood and blood forming organs diseases
E....	Mental and behavioural disorders
F....	Nervous system and sense organ diseases
G....	Circulatory system diseases
H....	Respiratory system diseases
J....	Digestive system diseases
K....	Genitourinary system diseases
L....	Pregnancy, childbirth and puerperium
M....	Skin and subcutaneous tissue diseases
N....	Musculoskeletal and connective tissue diseases
P....	Congenital anomalies
Q....	Perinatal conditions
R....	[D] Symptoms, signs, and ill-defined conditions
S....	Injury and poisoning
T....	Causes of injury and poisoning
U....	[X] External cause of morbidity and mortality
Z....	Unspecified conditions
Drugs	
A	Gastro-intestinal system drugs
B	Cardiovascular system drugs
C	Respiratory system drugs
D	Central nervous system drugs
E	Drugs for infectious diseases
F	Endocrine drugs
G	Obstetric, gynaecological, and urinary drugs
H	Malignant and immunosuppressant drugs
I	Nutrition and blood drugs
J	Musculoskeletal & joint drugs
K	Eye drugs
L	Ear, nose, and oropharynx drugs
M	Skin drugs
N	Immunology drugs and vaccines
O	Anaesthetic drugs
P	Appliances & reagents
Q	Incontinence appliances
S	Stoma appliances

Appendix 4. List of Read codes used to identify MUPS

Read code	Term
Functional Somatic Syndromes	
Irritable bowel syndrome	
J521.	Irritable bowel syndrome
J5210	Irritable bowel syndrome with diarrhoea
14CF.	History of irritable bowel syndrome
Eu453	[X]Psychogenic IBS
Non-cardiac chest pain	
R065B	[D]Non cardiac chest pain
1828.	Atypical chest pain
CFS	
F286.	Chronic fatigue syndrome (PVFS) / Myalgic encephalomyelitis
F2860	Mild chronic fatigue syndrome
F2861	Moderate chronic fatigue syndrome
F2862	Severe chronic fatigue syndrome
Eu460	[X]Fatigue syndrome
Tension type headache	
F2626	[X] Tension type headache
Temporomandibular joint disorder	
J0464	Temporomandibular joint-pain-dysfunction syndrome
Fibromyalgia	
N248.	Fibromyalgia
N2480	Myofascial pain syndrome
Somatoform disorder/ somatisation disorder	
Eu45.	[X]Somatoform disorders
Eu450	[X]Somatization disorder
Eu451	[X]Undifferentiated somatoform disorder
Eu454	[X]Persistent somatoform pain disorder
Eu45z	[X]Somatoform disorder, unspecified
Eu45y	[X]Other somatoform disorders
Hyperventilation syndrome	
R0601	[D]Hyperventilation
Chronic Pelvic pain	
R090G	[D] Pelvic pain
Conversion disorder	
Eu44.	[X]Conversion reaction
Eu44.	[X]Conversion hysteria
None-epileptic attack disorder	
Eu445	[X]Dissociative convulsions
Musculoskeletal symptoms	
Musculoskeletal Read codes are not shown, 3217 code were used	
Respiratory symptoms	
R060A	[D]Dyspnoea
173..	Dyspnoea - symptom
2322.	O/E - dyspnoea
1738.	Difficulty breathing
R0601	[D]Hyperventilation
232A.	O/E - hyperventilating
E2613	Psychogenic hyperventilation
Eu453	[X]Psychogenic hyperventilat
R062.	[D]Cough
171..	C/O - cough
171E.	Unexplained cough
171Z.	Cough symptom NOS
E2611	Psychogenic cough
Eu453	[X]Psychogenic cough
R068.	[D]Hiccough

Read code	Term
174..	Hiccough symptom
174Z.	Hiccough NOS
E2612	Psychogenic hiccough
Eu453	[X]Psychogenic hiccough
1742.	Hiccough present
Neurological symptoms	
R0442	[D]Loss of voice
R0441	[D]Aphonia
E2615	Psychogenic aphonia
E201z	Aphonia - hysterical
Eu444	[X]Psychogenic aphonia
R0440	[D]Voice disturbance, unspecified
R0443	[D]Change in voice
R0444	[D]Dysphonia
1C13.	Deafness symptom
Eu446	[X]Psychogenic deafness
1C13.	Deafness symptom
1C131	Unilateral deafness
1C132	Partial deafness
1C133	Bilateral deafness
E2012	Hysterical deafness
Eu446	[X]Psychogenic deafness
1B72.	Double vision
F482.	Diplopia (double vision)
F48y0	Blurred vision NOS
1B75.	Loss of vision
F4900	Unspecified blindness both eyes
F490z	Blindness both eyes NOS
F493.	Visual loss, both eyes unqualified
F49y.	Visual loss, one eye, unqualified
E2011	Hysterical blindness
F4901	Both eyes total visual impairment
R040.	[D]Headache
R0400	[D]Facial pain
R040z	[D]Pain in head NOS
1BA2.	Generalised headache
1BA3.	Unilateral headache
1BA4.	Bilateral headache
1BA5.	Frontal headache
1BA6.	Occipital headache
1BA7.	Parietal headache
1BA8.	Temporal headache
1BA9.	Sinus headache
1B1G.	C/O - a headache
E2781	Tension headache
1BB1.	Aching headache
1BB2.	Throbbing headache
1BB3.	Shooting headache
1BB4.	Morning headache
147E.	History of headache
Eu454	[X]Psychogenic headache
R0021	[D]Fainting
1B6..	Faint symptom
1B62.	Syncope/vasovagal faint
R0040	[D]Dizziness
1B5..	Dizziness symptom
1B5Z.	Incoordination symptom NOS
Eu46y	[X]Psychogenic syncope

Read code	Term
R003z	[D]Seizure NOS
R003.	[D]Convulsions
R0032	[D]Fit
R003z	[D]Convulsion NOS
1B64.	Convulsion - symptom
E2015	Hysterical seizures
R0072	[D]General weakness
1B3..	Weakness/ paralysis symptoms
1B320	Weakness of arm
1B321	Weakness of leg
1687.	Heavy feeling
1686.	Heavy legs
E2600	Psychogenic paralysis
1B37.	Loss of power in limb
R012.	[D]Gait abnormality
29LD.	Disorder of gait and/or balance present
R013.	[D]Lack of coordination
R0130	[D]Ataxia NOS
R0131	[D]Muscular incoordination
R0132	[D]Dysgraphia
E2014	Hysterical paralysis
R0003	[D]Loss of consciousness
Ry16.	[D]Slowness and poor responsiveness
1B1A.	Memory loss symptom
1B1A.	Amnesia symptom
1B1A0	Temporary loss of memory
E2017	Hysterical amnesia
R0206	[D]Numbness
1B44.	Has numbness
1B442	Numbness of limbs
R0203	[D]Tingling of skin
1B43.	Has tingling sensation
Cardiac symptoms	
R051.	[D]Palpitations
R0510	[D]Awareness of heart beat
R051z	[D]Palpitations NOS
181..	Palpitations
1812.	Palpitations
1813.	Bumping of heart
1814.	Fluttering of heart
181Z.	Palpitations NOS
R050.	[D]Tachycardia, unspecified
2426.	O/E - tachycardia
R065.	[D]Chest pain
R0650	[D]Chest pain, unspecified
R065B	[D]Non cardiac chest pain
R065z	[D]Chest pain NOS
1828.	Atypical chest pain
182Z.	Chest pain NOS
GI symptoms	
1CB4.	Feeling of lump in throat
R0720	[D]Difficulty in swallowing
194..	Swallowing symptoms
1942.	Difficulty swallowing solids
1943.	Difficulty swallowing liquids
1944.	Painful swallowing
R0700	[D]Nausea
198..	Nausea symptoms

Read code	Term
1982.	Nausea present
1983.	Morning nausea
198Z.	Nausea NOS
1984.	Upset stomach
R071.	[D]Heartburn
R0710	[D]Pyrosis
R071z	[D]Heartburn NOS
1955.	Heartburn symptom
R0711	[D]Waterbrash
1953.	Waterbrash
1952.	Regurgitation
195..	Indigestion symptoms
1954.	Indigestion
J16y4	Dyspepsia
1958.	Undiagnosed dyspepsia
E2644	Psychogenic dyspepsia
Eu453	[X]Psychogenic dyspepsia
195Z.	Indigestion symptom NOS
R0734	[D]Bloating
19B..	Bloating symptom
19B2.	Excessive flatulence
19B3.	Excessive belching
19B4.	Excessive eructation
19B5.	Excessive flatus
19BZ.	Wind NOS
E2640	Psychogenic aerophagy
19A..	Abdominal distension symptom
19A2.	Abdomen feels bloated
19A3.	Abdomen feels distended
19A4.	Abdomen feels swollen
19AZ.	Abd. distension symptom NOS
R0701	[D]Vomiting
199..	Vomiting symptoms
1992.	Vomiting
199Z.	Vomiting NOS
J16y5	Functional vomiting
Eu505	[X]Psychogenic vomiting
E2754	Psychogenic vomiting NOS
E2642	Cyclical vomiting - psychogenic
19C..	Constipation symptom
19C2.	Constipated
19CZ.	Constipation NOS
E2645	Psychogenic constipation
J520.	Constipation - functional
19F..	Diarrhoea symptoms
19F2.	Diarrhoea
19F3.	Spurious (overflow) diarrhoea
19FZ.	Diarrhoea symptom NOS
R076z	[D]Incontinence of faeces NOS
E2643	Psychogenic diarrhoea
Eu453	[X]Psychogenic diarrhoea
J525.	Functional diarrhoea
R090.	[D]Abdominal pain
R0900	[D]Abdominal tenderness
R0901	[D]Abdominal colic
R0902	[D]Colic NOS
R0904	[D]Abdominal cramps
R0905	[D]Epigastric pain

Read code	Term
R0906	[D]Umbilical pain
R0907	[D]Hypochondrial pain
R0908	[D]Suprapubic pain
R0909	[D]Pain in right iliac fossa
R090A	[D]Pain in left iliac fossa
R090B	[D]Groin pain
R090C	[D]Loin pain
R090D	[D]Abdominal migraine
R090E	[D]Recurrent acute abdominal pain
R090H	[D]Upper abdominal pain
R090K	[D]Left upper quadrant pain
R090L	[D]Left lower quadrant pain
R090M	[D]Right lower quadrant pain
R090N	[D]Nonspecific abdominal pain
R090z	[D]Abdominal pain NOS
1967.	Abdominal migraine - symptom
1968.	Abdominal discomfort
1969.	Abdominal pain
19690	Abdominal wall pain
F2622	Abdominal migraine
1969.	Abdominal pain
19690	Abdominal wall pain
1962.	Colicky abdominal pain
1963.	Non-colicky abdominal pain
1967.	Abdominal migraine - symptom
1971.	Central abdominal pain
1972.	Epigastric pain
1973.	Left subcostal pain
1974.	Right subcostal pain
1975.	Left flank pain
1976.	Right flank pain
1977.	Right iliac fossa pain
1978.	Left iliac fossa pain
1979.	Suprapubic pain
197A.	Generalised abdominal pain
197B.	Upper abdominal pain
197C	Lower abdominal pain
197D.	Right upper quadrant pain
E264z	Psychogenic gastrointestinal tract symptom NOS
Urogenital symptoms	
R0810	[D]Painful urination
R081.	[D]Dysuria
R0811	[D]Strangury
R081z	[D]Dysuria NOS
E2653	Psychogenic dysuria
Eu453	[X]Psychogenic dysuria
E2273	Impotence
Eu522	[X]Psychogenic impotence
E2276	Premature ejaculation
Eu524	[X]Premature ejaculation
K583.	Painful menstruation/ Dysmenorrhoea
Eu45y	[X]Psychogenic dysmenorrhoea
K592.	Excessive or frequent menstruation
K5920	Menorrhagia (heavy and prolonged)
K592z	Excessive or frequent menstruation NOS
K5921	Polymenorrhoea (period at shorter intervals <21 days)
K594.	Irregular menstrual cycle
K594z	Irregular menstrual cycle NOS

Read code	Term
K590.	Amenorrhoea (absence)
1A59.	C/O pelvic pain
R090G	[D] Pelvic pain
N33A0	Bony pelvic pain
R090G	[D]Pelvic and perineal pain
15D..	Dyspareunia
E2277	Psychogenic dyspareunia
Eu526	[X]Nonorganic dyspareunia
K28y7	Dyspareunia due to non psychogenic cause in the male
K580.	Dyspareunia due to non psychogenic cause in the female
15F..	Vaginismus
E2651	Psychogenic vaginismus
Eu525	[X]Nonorganic vaginismus
Eu525	[X]Psychogenic vaginismus
Autonomic symptoms	
R0261	[D]Flushing
R0262	[D]Excessive blushing
165..	Temperature symptoms
1B22.	Shaking
E2013	Hysterical tremor
R0103	[D]Tremor NOS
1B22.	Tremor symptom
Fatigue/ exhaustion	
Eu430	[X]Combat fatigue
R0071	[D]Fatigue
1682.	Fatigue
1688.	Exhaustion
168Z.	Tiredness symptom NOS
R0073	[D]Lethargy
168..	Lethargy - symptom
1683.	Tired all the time
1684.	Malaise/lethargy
1687.	Heavy feeling
168Z.	Tiredness symptom NOS

Appendix 5. List of Read codes for depression and anxiety disorders

Read code	Term
Eu412	[X]Mixed anxiety and depressive disorder
E2003	Anxiety with depression
E2112	Depressive personality disorder
1B17.	Depressed
62T1.	Puerperal depression
6G00.	Postnatal depression counselling
8CAa.	Patient given advice about management of depression
9H90.	Depression annual review
9H91.	Depression medication review
9H92.	Depression interim review
E03y2	Organic affective syndrome
E03y3	Unspecified puerperal psychosis
E11..	Affective psychoses
E110.	Manic disorder, single episode
E1100	Single manic episode, unspecified
E1101	Single manic episode, mild
E1102	Single manic episode, moderate
E1103	Single manic episode, severe without mention of psychosis
E1104	Single manic episode, severe, with psychosis
E1105	Single manic episode in partial or unspecified remission
E1106	Single manic episode in full remission
E110z	Manic disorder, single episode NOS
E111.	Recurrent manic episodes
E1110	Recurrent manic episodes, unspecified
E1111	Recurrent manic episodes, mild
E1112	Recurrent manic episodes, moderate
E1113	Recurrent manic episodes, severe without mention psychosis
E1114	Recurrent manic episodes, severe, with psychosis
E1115	Recurrent manic episodes, partial or unspecified remission
E1116	Recurrent manic episodes, in full remission
E111z	Recurrent manic episode NOS
E112.	Single major depressive episode
E1120	Single major depressive episode, unspecified
E1121	Single major depressive episode, mild
E1122	Single major depressive episode, moderate
E1123	Single major depressive episode, severe, without psychosis
E1124	Single major depressive episode, severe, with psychosis
E1125	Single major depressive episode, partial or unspec remission
E1126	Single major depressive episode, in full remission
E112z	Single major depressive episode NOS
E113.	Recurrent major depressive episode
E1130	Recurrent major depressive episodes, unspecified
E1131	Recurrent major depressive episodes, mild
E1132	Recurrent major depressive episodes, moderate
E1133	Recurrent major depressive episodes, severe, no psychosis
E1134	Recurrent major depressive episodes, severe, with psychosis
E1135	Recurrent major depressive episodes,partial/unspec remission
E1136	Recurrent major depressive episodes, in full remission
E1137	Recurrent depression
E113z	Recurrent major depressive episode NOS

Read code	Term
E114.	Bipolar affective disorder, currently manic
E1140	Bipolar affective disorder, currently manic, unspecified
E1141	Bipolar affective disorder, currently manic, mild
E1142	Bipolar affective disorder, currently manic, moderate
E1143	Bipolar affect disord, currently manic, severe, no psychosis
E1144	Bipolar affect disord, currently manic,severe with psychosis
E1145	Bipolar affect disord,currently manic, part/unspec remission
E1146	Bipolar affective disorder, currently manic, full remission
E114z	Bipolar affective disorder, currently manic, NOS
E115.	Bipolar affective disorder, currently depressed
E1150	Bipolar affective disorder, currently depressed, unspecified
E1151	Bipolar affective disorder, currently depressed, mild
E1152	Bipolar affective disorder, currently depressed, moderate
E1153	Bipolar affect disord, now depressed, severe, no psychosis
E1154	Bipolar affect disord, now depressed, severe with psychosis
E1155	Bipolar affect disord, now depressed, part/unspec remission
E1156	Bipolar affective disorder, now depressed, in full remission
E115z	Bipolar affective disorder, currently depressed, NOS
E116.	Mixed bipolar affective disorder
E1160	Mixed bipolar affective disorder, unspecified
E1161	Mixed bipolar affective disorder, mild
E1162	Mixed bipolar affective disorder, moderate
E1163	Mixed bipolar affective disorder, severe, without psychosis
E1164	Mixed bipolar affective disorder, severe, with psychosis
E1165	Mixed bipolar affective disorder, partial/unspec remission
E1166	Mixed bipolar affective disorder, in full remission
E116z	Mixed bipolar affective disorder, NOS
E117.	Unspecified bipolar affective disorder
E1170	Unspecified bipolar affective disorder, unspecified
E1171	Unspecified bipolar affective disorder, mild
E1172	Unspecified bipolar affective disorder, moderate
E1173	Unspecified bipolar affective disorder, severe, no psychosis
E1174	Unspecified bipolar affective disorder,severe with psychosis
E1175	Unspecified bipolar affect disord, partial/unspec remission
E1176	Unspecified bipolar affective disorder, in full remission
E117z	Unspecified bipolar affective disorder, NOS
E118.	Seasonal affective disorder
E11y.	Other and unspecified manic-depressive psychoses
E11y0	Unspecified manic-depressive psychoses
E11y1	Atypical manic disorder
E11y2	Atypical depressive disorder
E11y3	Other mixed manic-depressive psychoses
E11yz	Other and unspecified manic-depressive psychoses NOS
E11z.	Other and unspecified affective psychoses
E11z0	Unspecified affective psychoses NOS
E11z1	Rebound mood swings
E11z2	Masked depression
E11zz	Other affective psychosis NOS
E135.	Agitated depression
E204.	Neurotic depression reactive type
E290.	Brief depressive reaction
E290z	Brief depressive reaction NOS

Read code	Term
E291.	Prolonged depressive reaction
E2B..	Depressive disorder NEC
E2B0.	Postviral depression
E2B1.	Chronic depression
Eu3..	[X]Mood - affective disorders
Eu30.	[X]Manic episode
Eu300	[X]Hypomania
Eu301	[X]Mania without psychotic symptoms
Eu302	[X]Mania with psychotic symptoms
Eu30y	[X]Other manic episodes
Eu30z	[X]Manic episode, unspecified
Eu31.	[X]Bipolar affective disorder
Eu310	[X]Bipolar affective disorder, current episode hypomanic
Eu311	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu312	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu313	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu314	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Eu315	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu316	[X]Bipolar affective disorder, current episode mixed
Eu317	[X]Bipolar affective disorder, currently in remission
Eu31y	[X]Other bipolar affective disorders
Eu31z	[X]Bipolar affective disorder, unspecified
Eu32.	[X]Depressive episode
Eu320	[X]Mild depressive episode
Eu321	[X]Moderate depressive episode
Eu322	[X]Severe depressive episode without psychotic symptoms
Eu323	[X]Severe depressive episode with psychotic symptoms
Eu324	[X]Mild depression
Eu325	[X]Major depression, mild
Eu326	[X]Major depression, moderately severe
Eu327	[X]Major depression, severe without psychotic symptoms
Eu328	[X]Major depression, severe with psychotic symptoms
Eu329	[X]Single major depr ep, severe with psych, psych in remiss
Eu32A	[X]Recurr major depr ep, severe with psych, psych in remiss
Eu32y	[X]Other depressive episodes
Eu32z	[X]Depressive episode, unspecified
Eu33.	[X]Recurrent depressive disorder
Eu330	[X]Recurrent depressive disorder, current episode mild
Eu331	[X]Recurrent depressive disorder, current episode moderate
Eu332	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu333	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu334	[X]Recurrent depressive disorder, currently in remission
Eu33y	[X]Other recurrent depressive disorders
Eu33z	[X]Recurrent depressive disorder, unspecified
Eu34.	[X]Persistent mood affective disorders
Eu340	[X]Cyclothymia
Eu341	[X]Dysthymia
Eu34y	[X]Other persistent mood affective disorders
Eu34z	[X]Persistent mood affective disorder, unspecified
Eu3y.	[X]Other mood affective disorders
Eu3y0	[X]Other single mood affective disorders
Eu3y1	[X]Other recurrent mood affective disorders

Read code	Term
Eu3y2	[X]Premenstrual dysphoric disorder
Eu3yy	[X]Other specified mood affective disorders
Eu3z.	[X]Unspecified mood affective disorder
8G94.	Anxiety management training
E2...	Neurotic, personality and other nonpsychotic disorders
E20..	Neurotic disorders
E200.	Anxiety states
E2000	Anxiety state unspecified
E2001	Panic disorder
E2002	Generalised anxiety disorder
E2004	Chronic anxiety
E2005	Recurrent anxiety
E200z	Anxiety state NOS
E201.	Hysteria
E2010	Hysteria unspecified
E2011	Hysterical blindness
E2012	Hysterical deafness
E2013	Hysterical tremor
E2014	Hysterical paralysis
E2015	Hysterical seizures
E2016	Other conversion disorder
E2017	Hysterical amnesia
E2018	Hysterical fugue
E2019	Multiple personality
E201A	Dissociative reaction unspecified
E201B	Compensation neurosis
E201C	Phantom pregnancy
E201z	Hysteria NOS
E202.	Phobic disorders
E2020	Phobia unspecified
E2021	Agoraphobia with panic attacks
E2022	Agoraphobia without mention of panic attacks
E2023	Social phobia, fear of eating in public
E2024	Social phobia, fear of public speaking
E2025	Social phobia, fear of public washing
E2026	Acrophobia
E2027	Animal phobia
E2028	Claustrophobia
E2029	Fear of crowds
E202A	Fear of flying
E202B	Cancer phobia
E202C	Dental phobia
E202D	Fear of death
E202E	Fear of pregnancy
E202z	Phobic disorder NOS
E203.	Obsessive-compulsive disorders
E2030	Compulsive neurosis
E2031	Obsessional neurosis
E203z	Obsessive-compulsive disorder NOS
E205.	Neurasthenia - nervous debility
E206.	Depersonalisation syndrome
E207.	Hypochondriasis

Read code	Term
E20y.	Other neurotic disorders
E20y0	Somatization disorder
E20y1	Writer's cramp neurosis
E20y2	Other occupational neurosis
E20y3	Psychasthenic neurosis
E20yz	Other neurotic disorder NOS
E20z.	Neurotic disorder NOS
E21..	Personality disorders
E210.	Paranoid personality disorder
E211.	Affective personality disorder
E2110	Unspecified affective personality disorder
E2111	Hypomanic personality disorder
E2113	Cyclothymic personality disorder
E211z	Affective personality disorder NOS
E26..	Physiological malfunction arising from mental factors
E260.	Psychogenic musculoskeletal symptoms
E2600	Psychogenic paralysis
E2601	Psychogenic torticollis
E260z	Psychogenic musculoskeletal symptoms NOS
E261.	Psychogenic respiratory symptoms
E2610	Psychogenic air hunger
E2611	Psychogenic cough
E2612	Psychogenic hiccough
E2613	Psychogenic hyperventilation
E2614	Psychogenic yawning
E2615	Psychogenic aphonia
E261z	Psychogenic respiratory symptom NOS
E262.	Psychogenic cardiovascular symptoms
E2620	Cardiac neurosis
E2621	Cardiovascular neurosis
E2622	Neurocirculatory asthenia
E2623	Psychogenic cardiovascular disorder
E262z	Psychogenic cardiovascular symptom NOS
E263.	Psychogenic skin symptoms
E2630	Psychogenic pruritus
E263z	Psychogenic skin symptoms NOS
E264.	Psychogenic gastrointestinal tract symptoms
E2640	Psychogenic aerophagy
E2642	Cyclical vomiting - psychogenic
E2643	Psychogenic diarrhoea
E2644	Psychogenic dyspepsia
E2645	Psychogenic constipation
E264z	Psychogenic gastrointestinal tract symptom NOS
E265.	Psychogenic genitourinary tract symptoms
E2650	Psychogenic genitourinary tract malfunction unspecified
E2651	Psychogenic vaginismus
E2652	Psychogenic dysmenorrhea
E2653	Psychogenic dysuria
E265z	Psychogenic genitourinary tract symptom NOS
E266.	Psychogenic endocrine malfunction
E267.	Psychogenic symptom of special sense organ
E26y.	Other psychogenic malfunction

Read code	Term
E26y0	Bruxism (teeth grinding)
E26yz	Other psychogenic malfunction NOS
E26z.	Psychosomatic disorder NOS
E278.	Psychalgia
E2780	Psychogenic pain unspecified
E2781	Tension headache
E2782	Psychogenic backache
E278z	Psychalgia NOS
E28..	Acute reaction to stress
E280.	Acute panic state due to acute stress reaction
E281.	Acute fugue state due to acute stress reaction
E282.	Acute stupor state due to acute stress reaction
E283.	Other acute stress reactions
E2830	Acute situational disturbance
E2831	Acute posttrauma stress state
E283z	Other acute stress reaction NOS
E284.	Stress reaction causing mixed disturbance of emotion/conduct
E28z.	Acute stress reaction NOS
E29..	Adjustment reaction
E2900	Grief reaction
E292.	Adjustment reaction, predominant disturbance other emotions
E2920	Separation anxiety disorder
E2921	Adolescent emancipation disorder
E2922	Early adult emancipation disorder
E2923	Specific academic or work inhibition
E2924	Adjustment reaction with anxious mood
E2925	Culture shock
E292y	Adjustment reaction with mixed disturbance of emotion
E292z	Adjustment reaction with disturbance of other emotion NOS
E293.	Adjustment reaction with predominant disturbance of conduct
E2930	Adjustment reaction with aggression
E2931	Adjustment reaction with antisocial behaviour
E2932	Adjustment reaction with destructiveness
E293z	Adjustment reaction with predominant disturbance conduct
E294.	Adjustment reaction with disturbance emotion and conduct
E29y.	Other adjustment reactions
E29y0	Concentration camp syndrome
E29y1	Other post-traumatic stress disorder
E29y2	Adjustment reaction with physical symptoms
E29y3	Elective mutism due to an adjustment reaction
E29y4	Adjustment reaction due to hospitalisation
E29y5	Other adjustment reaction with withdrawal
E29yz	Other adjustment reactions NOS
E29z.	Adjustment reaction NOS
Eu4..	[X]Neurotic, stress - related and somoform disorders
Eu40.	[X]Phobic anxiety disorders
Eu400	[X]Agoraphobia
Eu401	[X]Social phobias
Eu402	[X]Specific (isolated) phobias
Eu403	[X]Needle phobia
Eu40y	[X]Other phobic anxiety disorders
Eu40z	[X]Phobic anxiety disorder, unspecified

Read code	Term
Eu41.	[X]Other anxiety disorders
Eu410	[X]Panic disorder [episodic paroxysmal anxiety]
Eu411	[X]Generalized anxiety disorder
Eu413	[X]Other mixed anxiety disorders
Eu41y	[X]Other specified anxiety disorders
Eu41z	[X]Anxiety disorder, unspecified
Eu42.	[X]Obsessive - compulsive disorder
Eu420	[X]Predominantly obsessional thoughts or ruminations
Eu421	[X]Predominantly compulsive acts [obsessional rituals]
Eu422	[X]Mixed obsessional thoughts and acts
Eu42y	[X]Other obsessive-compulsive disorders
Eu42z	[X]Obsessive-compulsive disorder, unspecified
Eu43.	[X]Reaction to severe stress, and adjustment disorders
Eu430	[X]Acute stress reaction
Eu431	[X]Post - traumatic stress disorder
Eu432	[X]Adjustment disorders
Eu433	[X]Acute post-traumatic stress disorder follow military comb
Eu434	[X]Chron post-traumatic stress disorder follow military comb
Eu435	[X]Delayed post-traumat stress disorder follow military comb
Eu43y	[X]Other reactions to severe stress
Eu43z	[X]Reaction to severe stress, unspecified
Eu44.	[X]Dissociative [conversion] disorders
Eu440	[X]Dissociative amnesia
Eu441	[X]Dissociative fugue
Eu442	[X]Dissociative stupor
Eu443	[X]Trance and possession disorders
Eu444	[X]Dissociative motor disorders
Eu445	[X]Dissociative convulsions
Eu446	[X]Dissociative anaesthesia and sensory loss
Eu447	[X]Mixed dissociative [conversion] disorders
Eu44y	[X]Other dissociative [conversion] disorders
Eu44z	[X]Dissociative [conversion] disorder, unspecified
Eu45.	[X]Somatoform disorders
Eu450	[X]Somatization disorder
Eu451	[X]Undifferentiated somatoform disorder
Eu452	[X]Hypochondriacal disorder
Eu453	[X]Somatoform autonomic dysfunction
Eu454	[X]Persistent somatoform pain disorder
Eu455	[X]Globus pharyngeus
Eu45y	[X]Other somatoform disorders
Eu45z	[X]Somatoform disorder, unspecified
Eu46.	[X]Other neurotic disorders
Eu460	[X]Neurasthenia
Eu461	[X]Depersonalization - derealization syndrome
Eu46y	[X]Other specified neurotic disorders
Eu46z	[X]Neurotic disorder, unspecified
ZN114	Anxiety Management
ZS7C7	Post-traumatic mutism
1B17.	Depressed
62T1.	Puerperal depression